Drug Comparison Charts www.RxFiles.ca

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Other Online EBM Resources/Links:

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

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

Online Extras

Guidelines, Evidence and Patients

- Guidelines provide guidance based on evidence, clinical experience and someone's values and preferences.
  - Considerations: Evidence
    - How current? Has level/strength of evidence (evidence quality) been assessed for recommendations? (e.g. May have more confidence if high quality, multiple, trials.)
    - What outcomes are evaluated? Are they patient orientated or surrogate?
    - Has evidence been allowed to inform pre-existing assumptions, biases and beliefs?
    - Is the evidence applicable to your patient(s)?
  - Clinical experience / consensus
    - Is expert opinion, and extent of agreement acknowledged
  - Conflicts of Interest (https://www.cmaj.ca/content/193/2/E49)
    - Are conflicts of interest disclosed
    - Conflicts may be financial or non-financial
    - Methods should be transparent and rigorous to inform objectively on best available evidence
  - Values
    - In what way are values and preferences included?
    - Who's values: Patient? Society? Payer? Professional?
  -
- Overall assessment:
  - Look for transparency, evidence ratings, peer review, conflicts of interest
  - Do the guidelines allow for, and enable, shared decision making with patients?
- If the guidelines don't apply, don't apply them! Almost all guidelines contain a chapter/disclaimer noting that any recommendations must be assessed and individualized for the patient in front of you. Recommendations are often intended to apply to a majority of patients, but may not be suitable for the patient in front of you. If so, document reason for your decision.

EBM	1
Evidence Based Medicine	1
NNH	1
NNT	1
Precision	1
Validity	1

RxFiles: Evidence Based Medicine (EBM) Overview - References

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1◦=primary prevention **2◦**=secondary prevention **AAA**=abdominal aortic aneurysm **ACR**=albumin to creatinine ratio **Apo**=apolipoprotein **BP**=blood pressure **BMI**=body mass index **COPD**=chronic obstructive pulmonary disease **CKD**=chronic kidney disease **CV**=cardiovascular disease **CVD**= cardiovascular disease **DM**=diabetes mellitus **eGFR**=estimated glomerular filtration rate **HDL**=high density lipoprotein **HTN**=hypertension **Na+**=sodium **NaCl**=sodium chloride **NNT**=number needed to treat **LDL**=low density lipoprotein **K+**=potassium **RAAS**=renin angiotensin aldosterone system **SBP**=systolic blood pressure **T1DM**=Type 1 Diabetes Mellitus **T2DM**=Type 2 Diabetes Mellitus **TG**=triglycerides **TIA**=transient ischemic attack **Tx**=treatment

AHA/ACC BLOOD CHOLESTEROL Targets: tailor statin-intensity to patient risk profile, use LDL-C to assess therapy / adherence

FRAMINGHAM RISK SCORE (available at the Canadian Cardiovascular Society website: https://www.ccs.ca/images/Guidelines/Tools_and_Calculators_En/FRS_eng_2017_fnl1.pdf)

FRAMINGHAM RISK SCORE (FRS)

Estimation of 10-year Cardiovascular Disease (CVD) Risk

Date: _____

Patient's Name: _____

Step 1[1]

In the "points" column enter the appropriate value according to the patient's age, HDL-C, total cholesterol, systolic blood pressure, and if they smoke or have diabetes. Calculate the total points.

Risk Factor	Risk Points				Points
	Men		Women		
Age					
30-34	0		0		
35-39	2		2		
40-44	5		4		
45-49	7		5		
50-54	8		7		
55-59	10		8		
60-64	11		9		
65-69	12		10		
70-74	14		11		
75+	15		12		
HDL-C (mmol/L)					
>1.6	-2		-2		
1.3-1.6	-1		-1		
1.2-1.29	0		0		
0.9-1.19	1		1		
<0.9	2		2		
Total Cholesterol					
<4.1	0		0		
4.1-5.19	1		1		
5.2-6.19	2		3		
6.2-7.2	3		4		
>7.2	4		5		
Systolic Blood Pressure (mmHg)	Not Treated	Treated	Not Treated	Treated	
<120	-2	0	-3	-1	
120-129	0	2	0	2	
130-139	1	3	1	3	
140-149	2	4	2	5	
150-159	2	4	4	6	
160+	3	5	5	7	
Smoker Yes	4		3		
Smoker No	0		0		
Diabetes Yes	statin-indicated condition				
Diabetes No	0		0		
Total Points					

1 Adapted from: D'Agostino RB et al.(i). General cardiovascular risk profile for use in primary care. The Framingham Heart Study. Circ 2008;117:743-53.
2 Adapted from: Genest J et al.(i). 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult. Can J Cardiol. 2009;25(10):567-579.
3 Adapted from: Anderson T et al.(i). 2012 Update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2013;29(2):151-167.

[t] apoB: apolipoprotein B stat, CVD: cardiovascular disease, FRS: Framingham Risk Score, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol.
* Statins indicated as initial therapy
** Consider LDL-C < 1.8 mmol/L for subjects with acute coronary syndrome (ACS) within past 3 months

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Step 2[1]

Using the total points from Step 1, determine the 10-year CVD risk (%).*

Total Points	10-Year CVD Risk (%)*	
	Men	Women
-3 or less	<1	<1
-2	1.1	<1
-1	1.4	1.0
0	1.6	1.2
1	1.9	1.5
2	2.3	1.7
3	2.8	2.0
4	3.3	2.4
5	3.9	2.8
6	4.7	3.3
7	5.6	3.9
8	6.7	4.5
9	7.9	5.3
10	9.4	6.3
11	11.2	7.3
12	13.3	8.6
13	15.6	10.0
14	18.4	11.7
15	21.6	13.7
16	25.3	15.9
17	29.4	18.51
18	>30	21.5
19	>30	24.8
20	>30	27.5
21+	>30	>30

* Double cardiovascular disease risk percentage for individuals between the ages of 30 and 59 without diabetes if the presence of a positive history of premature cardiovascular disease is present in a first-degree relative before 55 years of age for men and before 65 years of age for women. This is known as the modified Framingham Risk Score.[3]

Step 3[1]

Using the total points from Step 1, determine heart age (in years).

Heart Age, y	Men	Women
<30	<0	<1
30	0	
31		1
32	1	
34	2	2
36	3	3
38	4	
39		4
40	5	
42	6	5
45	7	6
48	8	7
51	9	8
54	10	
55		9
57	11	
59		10
60	12	
64	13	11
68	14	12
72	15	
73		13
76	16	
79		14
>80	≥17	15+

Step 4[2,3]

Using 10-year CVD risk from Step 2, determine if patient is Low, Moderate or High risk.[t] Indicate Lipid and/or Apo B targets

Risk Level[t]	Initiate Treatment If:	Primary Target (LDL-C)	Alternate Target
High FRS ≥20%	• Consider treatment in all *(Strong, High)*	• ≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, Moderate)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, High)*
Intermediate FRS 10-19%	• LDL-C ≥3.5 mmol/L *(Strong, Moderate)* • For LDL-C <3.5 mmol/L consider if: • Apo B ≥1.2 g/L • OR Non-HDL-C ≥4.3 mmol/L *(Strong, Moderate)* • *Men ≥50 and women ≥60 with 1 risk factor: low HDL-C, impaired fasting glucose, high waist circumference, smoker, hypertension*	• ≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, Moderate)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, Moderate)*
Low FRS <10%	• statins generally not indicated	• statins generally not indicated	• statins generally not indicated
Statin-indicated conditions**	• *Clinical atherosclerosis** • *Abdominal aortic aneurysm* • *Diabetes mellitus Age ≥ 40 years 15-Year duration for age ≥ 30 years (DM1) Microvascular disease* • *Chronic kidney disease (age ≥ 50 years) eGFR <60 mL/min/1.73 m2 or ACR > 3 mg/mmol*		

Lipid targets LDL-C: _____ or Apo B: _____

NEW ZEALAND PRIMARY CARE HANDBOOK 2012 – 5 Year CVD Risk Assessment Tables
Available at: https://www.health.govt.nz/system/files/documents/publications/nz-primary-care_handbook_2012.pdf
- Quick & easy way to estimate **heart & stroke risk**. Based on Framingham

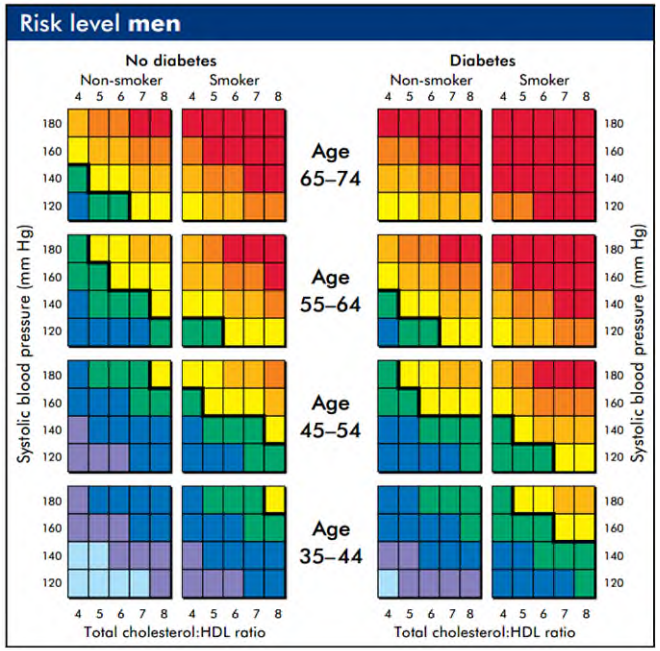
How to use the Charts

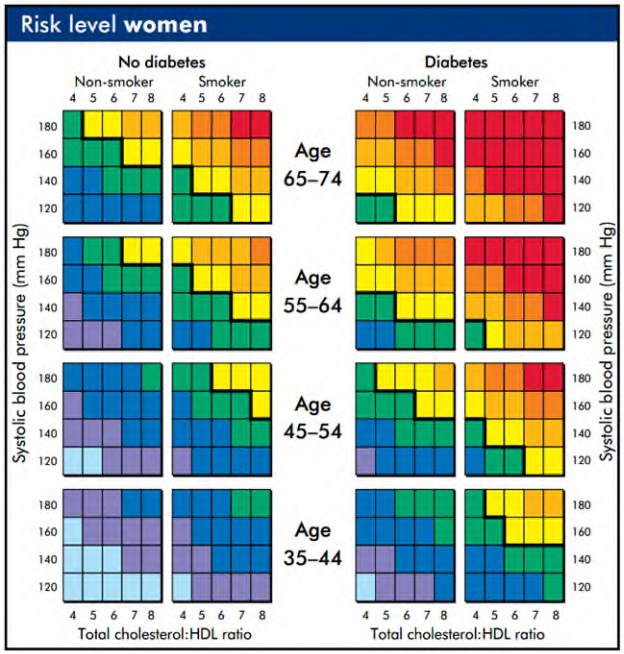
- Identify the chart relating to the person's sex, diabetic status, smoking history and age
- Within the chart choose the cell nearest to the person's age, systolic blood pressure (SBP) and total cholesterol (TC) TC:HDL ratio. For example, the lower left cell contains all non-smokers without diabetes who are 35–44 years and have a TC:HDL ratio of less than 4.5 and a SBP of less than 130 mm Hg. People who fall exactly on a threshold between cells are placed in the cell indicating higher risk
- The risk charts now include values for SBP alone, as this is the most informative of conventionally measured blood pressure parameters for cardiovascular risk. Diastolic pressures may add some predictive power, especially at younger ages (eg, a diastolic pressure consistently >100 mm Hg in a patient with SBP values between 140 and 170 mm Hg)

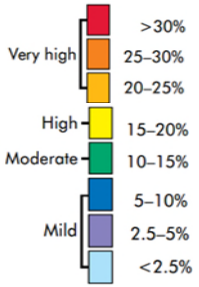
a) NNT = Number needed to treat
Based on the conservative estimate that each intervention:
ASA ASPIRIN, **BP treatment** (lowering SBP by 10 mmHg) or **lipid** modification (↓ LDL by 20%) reduces cardiovascular risk by about 25% over 5 years.

b) Cardiovascular events are defined as MI, new angina, ischemic stroke, TIA, PVD, HF & CV death.

Note: 15% on this **5 year** CVD heart & stroke risk tool is approximately equal to 20% on the common **10 year** Framingham CAD risk tool.







Risk level: 5-year CVD risk (fatal and non-fatal)	Benefits: NNT for 5 years to prevent one event (CVD events prevented per 100 people treated for 5 years)		
	1 intervention (25% risk reduction)	2 interventions (45% risk reduction)	3 interventions (55% risk reduction)
30%	13 (7.5 per 100)	7 (14 per 100)	6 (16 per 100)
20%	20 (5 per 100)	11 (9 per 100)	9 (11 per 100)
15%	27 (4 per 100)	15 (7 per 100)	12 (8 per 100)
10%	40 (2.5 per 100)	22 (4.5 per 100)	18 (5.5 per 100)
5%	80 (1.25 per 100)	44 (2.25 per 100)	36 (3 per 100)

Cardiovascular Disease (CVD) Risk Asseessment Tools:

1) http://www.cvriskcalculator.com/ [AHA/ACC, 2013] Considers: age, gender, race, total cholesterol, HDL cholesterol, SBP, DBP, treatment of hypertension, diabetes, smoking status
2) http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/ [ACC, 2018] Considers: age, sex, race, SBP, DBP, total cholesterol, HDL, LDL, diabetes, smoking status, treatment of hypertension, use of statin, use of aspirin
3) http://www.myhealthcheckup.com [Canada] Considers: age, gender, height, weight, waist measurement, total cholesterol, LDL, HDL, SBP, DBP, blood glucose; treatment of: hypertension, high cholesterol or diabetes; existence of: heart disease, stroke/TIA, PVD, family hx (CVD or diabetes), exercise, smoking status
4) https://www.projectbiglife.ca/cardiovascular-disease [Canada] Considers: age, sex, smoking (amount), alcohol consumption (amount), nutrition, physical activity, education level, weight, height, diabetes, hypertension
5) https://www.framinghamheartstudy.org/ [USA: 10year and 30year risk assessment available; interactive and excel spreadsheet] Considers: age, sex, diabetes, smoking status, SBP, total cholesterol, HDL, BMI
6) http://chd.bestsciencemedicine.com/calc2.html [4 different calculators; data from USA, UK, New Zealand]
7) http://www.reynoldsriskscore.org/ [UK] Considers: age, gender, BP, cholesterol, smoking status, hsCRP, family hx (MI)
8) http://www.jbs3risk.com/ [UK] Considers: age, gender, ethnicity, BMI, townsend, total cholesterol, HDL, SBP

Cardiovascular Risk Factors	2
CVD Risk Assessment	2
Framingham Risk Assessment	2
Targets	2
Lipid	2
Blood Pressure	2
Hypertension	**2**

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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

STABLE ANGINA: Ischemia Relief Drug Comparison Chart: Other Agents (not available in Canada or not indicated for stable angina in Canada)

GENERIC TRADE	COMMENTS	CONTRAINDICATIONS CI /ADVERSE EVENTS AE /DRUG INTERACTIONS DI	INITIAL, USUAL & MAXIMUM DOSE	$/30 DAY
LATE NA CHANNEL INHIBITOR:[37-47] Mechanism unknown, theories: ↓ oxygen demand (via inhibition sodium channel which indirectly ↓ calcium overload [which ↓ myocardial tension ↑ myocardial bloodflow]); partially inhibits fatty acid oxidation				
Ranolazine **CORZYNA** RANEXA 500, 1000mg ER tab ✗ ⊗ PL -**new** in Canada (available in US) 375, 500, 750mg ER tab (available in EU)	• 2nd line agent for angina prophylaxis in combination with BB AHA2012 (IIa,A) or CCB, ESC 2013 (IIa,b) or monotherapy (if BB ineffective, CI or intolerable).AHA 2012(IIa,B) • Approved in the US & Europe for stable long-term stable angina prophylaxis. • No effect on disease on morbidity/mortality in stable angina. • Ranolazine add-on therapy vs placebo ↓ angina episodes/wk in a meta-analysis (N=3, n=2004[39] CARISA, [40] ERICA, [41] TERISA) by MD -0.66 (-0.97 to -0.35). No difference with monotherapy vs placebo. ↑ non-serious AE with ranolazine add-on therapy or monotherapy vs placebo (RR 1.2-1.5).Cochrane'17 • ? Benefit diabetes patients, ↓ HbA1c vs placebo -0.28 to -0.7 (other important diabetes outcomes not assessed) [44]	**CI:** cirrhosis, CrCl <30 mL/min, **strong CYP3A inhibitors or inducers** **AE:** dizziness, headache, nausea, constipation, peripheral edema, asthenia, QTc prolongation **DI:** ↑ ranolazine effect: CYP3A4 inhibiters (non-DHP CCB, erythromycin [max ranolazine 500 mg BID]) & Pgp inhibitors: (cyclosporine); ↑ effect of: simvastatin (max simavstatin20 mg/day), digoxin, TCAs; QTc prolonging agents **M**: sx, HR, BP, & AE (minimal impact on HR & BP)	Increase dose q2-4wks until symptom relief. Ranolazine 500mg BID (1000mg BID) EU: Ranolazine 375mg BID (750mg BID)	$260 ($490)
SELECTIVE SINUS NODE I(f) INHIBITOR: [48-53] ↓ oxygen demand (↓HR by inhibiting sinus node *I(f)* pacemaking current)), ↑ oxygen supply (↑ diastolic time & coronary perfusion) ✓Long term management of stable angina[48] EMA				
Ivabradine LANCORA ☎ ✆ 5ᶜ, 7.5 mg tabs PL **New** in **Canada** (available EU & US)	• 2nd line agent for angina prophylaxis in combination with BB EMA (or CCB) ESC'13 (IIa,B) if suboptimal control on monotherapy. • Approved in Canada & the US for HF-rEF (≤ 35%); both monographs state no benefit in CAD ± stable HF. Approved in Europe for HF and long-term stable angina prophylaxis. • No effect on disease on morbidity/mortality in stable angina (±HF). [49] SIGNIFY [49] BEAUTIFUL • Ivabradine 5-10 mg/d monotherapy prolongs time to angina symptoms onset vs placebo and was non-inferior vs BB (atenolol 100 mg daily) INITIATE or CCB (amlodipine 10 mg daily). • Ivabradine + atenolol 50 mg/d prolongs time to angina symptom onset vs placebo but no difference in angina attacks/week.ASSOCIATE • ? safety as ↑ death/nonfatal MI HR 1.18 (1.03-1.35) in pre-specified CCS class II-IV subgroup vs Pl & ↑ AE leading to withdrawal; but, mean dose (8.2mg BID) ↑ than max dose.[49] SIGNIFY	**CI:** ↓**HR** (<77 bpm CDN, <70 bpm EMA), heart rhythm disorder, non-DHP CCB, strong CYP3A4i, severe hepatic disease, & existing prolonged QT interval. **AE**: HA, dizziness, visual disturbance (e.g., blurred vision, phosphenes [transient enhanced brightness]; resolve spontaneously OR reversible with D/C) ↓HR, AF; ↑ risk: [>75 yr] SHIFT **DI:** ↑ ivabradine effect (CYP3A4 inhibitors): fluconazole, clarithromycin, ritonavir; ↓ ivabradine effect (CYP3A4 induction): rifampin, phenytoin; QTc prolonging agents **M**: sx, HR, BP, & AE (minimal impact on BP)	Increase dose q2-4 wks until symptom relief. Ivabradine 2.5-5mg BID (7.5mg BID) with food	$39-69 ($118)
POTASSIUM CHANNEL ACTIVATOR & NITRATE-DERIVATIVE:[54-59] ↑ oxygen supply by dilating coronary arteries				
Nicorandil 10, 20mg tabs (available EU)	• 2nd line agent for angina prophylaxis in combination with BB or CCB ESC'13 (IIa,B) if suboptimal control on monotherapy. • Nicorandil vs placebo (+background antianginal tx) ↓ composite CV death, nonfatal MI, admission for cardiac chest pain HR 0.83 (p values not reported for individual outcomes); angina sx not reported. ↑ withdrawal (39% vs 32%), mainly due to headaches with nicorandil).[55] IONA • Other small n<150, RCTs with mixed anti-ischemic results (e.g., angina frequency).[54,56-59]	**CI:** cardiogenic shock, HF **AE**: **headache**, dizziness, flushing, hypotension, ulcerations (oral, anal, GI) **DI:** ↑ nicorandil effect/AEs: PDEi inhibitors **M**: sx, HR, BP, & AE	Increase dose q2 wks until symptom relief. Nicorandil 10mg BID (20mg BID)	NA
3-KETOACYL-CoA THIOLATE INHIBITOR: Mechanism unknown, theories: ↑ oxygen supply by increasing coronary flow reserve; improve cellular tolerance to ischemia via inhibition of fatty acid metabolism				
Trimetazidine 20 mg tab (available EU)	• 2nd line agent for angina prophylaxis in combination with BB or CCB ESC'13 (IIb,B) if suboptimal control on monotherapy. • Insufficient data on trimetazidine's affect on morbidity/mortality in stable angina. • Trimetazidine ↓ angina attacks/wk by ~1.5, ↓ nitrate use/wk by ~1.5 units/week in but ↑heterogeneity (I^2 >90%).[60]	**CI:** Parkinson's dx, motion disorders, renal impairment **AE**: movement disorders, headache, fatigue, dizziness, GI upset (nausea, pain, constipation) **M**: sx, HR, BP, & AE (minimal impact on HR & BP)	Trimetazidine 10 mg daily (20mg TID)	NA

A note on stress testing - there are multiple strategies. The stress may refer to exercise, or pharmacological 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
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 -**duration: ~5-15mins** -management: CCB (DHP or non-DHP) ± NTG; BB should be avoided (due to unopposed alpha agonism).[35] Encourage smoking cessation	-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**
Epidemiology	-??? (no widely utilized diagnostic criteria) ESC2013, [29]. ~ 40% coronary angiograms normal/near normal coronary arteries[30]	
	-smoking is a risk factor	-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

Angina Online Appendix:

RISK ASSESSMENT: Stable Angina [AHA '12]

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).

AN APPORACH TO DECISION MAKING: [ESC '13]

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

Exercise stress ECG[b]	High risk Intermediate risk Low risk	CV mortality >3%/year. CV mortality between 1 and 3%/year. CV mortality <1%/year.
Ischaemia imaging	High risk Intermediate risk Low 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). Area of ischaemia between 1 to 10% or any ischaemia less than high risk by CMR or stress echo. No ischaemia.
Coronary CTA[c]	High risk Intermediate rick Low risk	Significant lesions of high risk category (three-vessel disease with proximal stenoses, LM, and proximal anterior descending CAD). Significant lesion(s) in large and proximal coronary artery(ies) but not high risk category. 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.

(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 [AHA '14]

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)

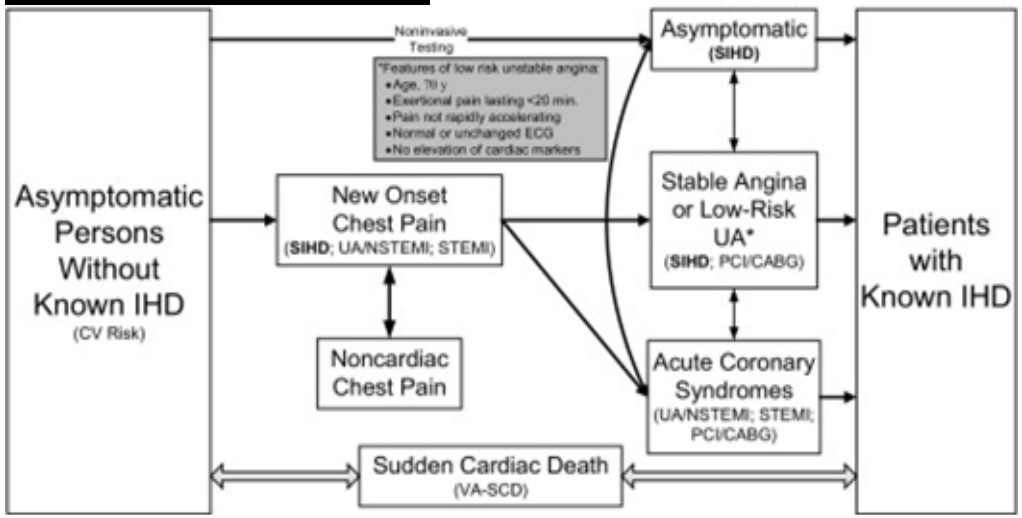
TIMI (Thrombolysis in Myocardial Infarction) Risk Score: derived from TIMI IIB trial and validated in TIMI IIb and ESSENCE trials; used to predict composite all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization within 14 days. (http://www.timi.org/index.php?page=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

SPECTRUM OF CORONARY ARTERY DISEASE AHA '12



Angina	**3**
Chest Pain	3
Chronic Stable Angina	3
Coronary Artery Disease	3
Microvascular Angina	3
Stable Ischemic Heart Dx	3
Unstable Angina	**3**
Vasospastic Angina	3
ADALAT	4
Amlodipine	4
Angina	**4**
Angina	**4**
Atenolol	4
Bisoprolol	4
BLOCADREN	4
CARDIZEM	4
Carvedilol	4
COREG	4
CORGARD	4
CORZYNA	4
Diltiazem	4
Felodipine	4
IMDUR	4
INDERAL	4
ISOPTIN	4
ISORDIL	4
Isosorbide	4
Ivabradine	4
Labetalol	4
LANCORA	4
LOPRESOR	4
Metoprolol	4

MINITRAN	4
MONOCOR	4
Nadolol	4
Nicorandil	4
Nifedipine	4
NITRO-DUR, NITROL	4
Nitroglycerin	4
NITROLINGUAL	4
NITROSTAT	4
NORVASC	4
PLENDIL	4
Propranolol	4
RANEXA	4
Ranolazine	4
RENEDIL	4
TENORMIN	4
TIAZAC	4
Timolol	4
TRANDATE	4
TRANSDERM NITRO	4
Trimetazidine	4
TRINIPATCH	4
Unstable Angina	**4**
Verapamil	4

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150.

ACCUPRIL	5
ACE Inhibitor	**5**
Aliskiren	5
ALTACE	**5**
Antihypertensive	5
ARB	**5**
ATACAND	**5**
AVALIDE	5
AVAPRO	5
Azilsartan	5
Benazepril	5
Candesartan	5
CAPOTEN	5
Captopril	**5**
Cilazapril	5
COVERSYL / PLUS	5
COZAAR	5
DIOVAN	**5**
EDARBI	5
EDARBYCLOR	5
Enalapril	**5**
Eprosartan	5
Fosinopril	5
Hypertension	5
HYZAAR	5
INHIBACE	5
Irbesartan	5
Lisinopril	**5**
Losartan	5
LOTENSIN	5
MAVIK	5
MICARDIS	5
MONOPRIL	5
Olmesartan	5
OLMETEC	5
Perindopril +/- Indapamide	**5**
PRINIVIL	**5**
PRINZIDE	5
Quinapril	5
Ramipril	**5**
RASILEZ	5
TEKTURNA	5
Telmisartan	5
TEVETEN	5
Trandolapril	**5**
Valsartan	**5**
VASERETIC	5
VASOTEC	**5**
ZESTORETIC	5
Blood Pressure	5
ZESTRIL	**5**

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

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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.
FDA Nov/18: Sandoz Inc. Issues Voluntary Nationwide Recall of One Lot of **Losartan Potassium and Hydrochlorothiazide** Due to the Detection of Trace Amounts of NDEA (N-Nitrosodiethylamine) Impurity Found in the Active Pharmaceutical Ingredient (API)
FDA Nov/18: All **Amlodipine/Valsartan** Combination Tablets and **Amlodipine/Valsartan/Hydrochlorothiazide** Combination Tablets by Teva Pharmaceuticals USA: Recall - Due to an Impurity Detected Above Specification Limits in an Active Pharmaceutical Ingredient (API)
FDA Nov/18: Sandoz Inc. Issues Voluntary Nationwide Recall of One Lot of **Losartan Potassium and Hydrochlorothiazide** Due to the Detection of Trace Amounts of NDEA (N-Nitrosodiethylamine) Impurity Found in the Active Pharmaceutical Ingredient (API)
FDA Nov/18: All **Amlodipine/Valsartan Combination** Tablets and **Amlodipine/Valsartan/Hydrochlorothiazide** Combination Tablets by Teva Pharmaceuticals USA: Recall - Due to an Impurity Detected Above

Specification Limits in an Active Pharmaceutical Ingredient (API)
FDA Jan/19: **Losartan Potassium Tablets**, USP and **Losartan Potassium and Hydrochlorothiazide Tablets**, USP by Torrent Pharmaceuticals: Recall Due to the Detection of N-nitrosodiethylamine (NDEA)
FDA Dec/18: **Losartan Potassium Tablets**, USP by Torrent Pharmaceuticals Limited: Due to the detection of trace amounts of an unexpected impurity, N-nitrosodiethylamine (NDEA), found in the active pharmaceutical ingredient (API) was just added to the FDA Recalls webpage.
FDA Jan/19: **Irbesartan and Irbesartan/Hydrochlorothiazide** (HCTZ) Tablets by Prinston Pharmaceutical: Recall - Due to Detection of a Trace Amount of Unexpected Impurity, N-nitrosodiethylamine (NDEA)
Jan/19 Prinston Pharmaceutical Inc has recalled one consumer-level lot of irbesartan and seven lots of irbesartan hydrochlorothiazide (HCTZ) tablets because of the presence of the probable carcinogen N-nitrosodiethylamine (NDEA), marking the latest recall of tainted sartan products produced in the United States.
FDA Mar/19: **Valsartan Tablets USP, 160 mg** by American Health Packaging: Recall - Due to Detection of N-Nitrosodiethylamine (NDEA) Impurity
FDA Mar/19 on Friday announced that India's Hetero Labs was recalling 87 lots of **losartan potassium tablets** distributed by Camber Pharmaceuticals because they contain the impurity, N-Nitroso-N-methyl-4-aminobutyric Acid(NMBA).
FDA Mar/19: **Losartan Potassium** Tablets by Legacy Pharmaceutical Packaging: Recall - Due to The Detection of Trace Amounts Of N-Nitroso N-Methyl 4-Amino Butyric Acid Impurity Found in The Active Pharmaceutical Ingredient
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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).
Health Canada Sep/18: is advising Canadians that a second impurity, called N-nitrosodiethylamine (NDEA) has been found in valsartan manufactured by Zhejiang Huahai Pharmaceuticals in China. All drugs containing valsartan manufactured by Zhejiang Huahai Pharmaceuticals have already been recalled in Canada after the first impurity, N-nitrosodimethylamine (NDMA), was identified earlier this summer.

Health Canada Nov/18: Mylan Pharmaceuticals ULC is voluntarily **recalling four lots of Mylan-Valsartan tablets** (40 mg, 80 mg, 160 mg and 320 mg strength) after testing found low levels of an impurity, N-nitrosodiethylamine (NDEA).

Health Canada Nov/18: Mylan **Pharmaceuticals ULC is voluntarily recalling four lots of Mylan-Valsartan tablets** (40 mg, 80 mg, 160 mg and 320 mg strength) after testing found low levels of an impurity, N-nitrosodiethylamine (NDEA).

Health Canada Dec/18 tested 48 samples (**certain sartan drugs**: **valsartan, candesartan, irbesartan, losartan, and olmesartan**) representing 43 different products and did not identify any new safety concerns. Of the 48 samples, six valsartan samples representing four products were found to contain levels of impurities that were, on average, higher than what is considered to be reasonably safe. All four of the products have already been recalled from the Canadian market.

Health Canada Mar/19 is advising Canadians that Pro Doc Limitée is voluntarily recalling two lots of **irbesartan** tablets because of a nitrosamine impurity, N-nitrosodiethylamine (NDEA).

Health Canada Mar/19 is advising Canadians that multiple lots of **Losartan-containing drugs** are being voluntarily recalled by Teva Canada, Apotex Inc., Pharmascience Inc., and Pro Doc Limitée because of the potential for a nitrosamine impurity, N-Nitroso-N-methyl-4-aminobutyric acid (NMBA). NMBA is potentially a human carcinogen, which means that long-term exposure could increase the potential risk of cancer.

Health Canada Apr/19 is advising Canadians that Auro Pharma Inc. is voluntarily recalling one lot of Auro-Irbesartan/hydrochlorothiazide (HCT) combination tablets because of a nitrosamine impurity, N-nitrosodiethylamine (NDEA).

Health Canada May/2021 is informing Canadians that several companies are recalling multiple lots of irbesartan, losartan and valsartan drug products after tests found an azido impurity above the acceptable limit.

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Acebutolol	6
Antihypertensive	6
Atenolol	**6**
Beta-blocker	**6**
Bisoprolol	**6**
BLOCADREN	6
BREVIBLOC	6
BYSTOLIC	6
Carvedilol	**6**
COREG	**6**
CORGARD	6
Esmolol	6
Hypertension	6
INDERAL	**6**
Intrinsic Sympathetic Activity	6
ISA	6
Labetalol	**6**
LOPRESOR	**6**
MONITAN	6
MONOCOR	**6**
Nadolol	6
Nebivolol	6
Oxprenolol	6
Pindolol	6
Propranolol	**6**
SECTRAL	**6**
SOTACOR	**6**
Sotalol	6
TENORETIC	6
TENORMIN	6
Timolol	**6**
TRANDATE	**6**
TRASICOR	6
VISKAZIDE	6
VISKEN	6
Blood Pressure	6
BETALOC	**6**
Metoprolol	**6**

BETA-BLOCKER (BB): Comparison Chart

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ADALAT	7
Amlodipine	**7**
Angina	7
Antihypertensive	7
CADUET	7
Calcium Channel Blocker	**7**
CARDIZEM	7
Coronary Artery Disease	7
Diltiazem	7
Felodipine	7
Hypertension	7
ISOPTIN	7
Nifedipine	7
NORVASC	**7**
PAD	7
PLENDIL	7
Raynaud's	7
RENEDIL	7
TARKA	7
TIAZAC	7
TWYNSTA	7
Verapamil	**7**
VIACORAM	7
Blood Pressure	7

CALCIUM CHANNEL BLOCKER (CCB): Comparison Chart

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CATAPRES	8
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Doxazosin	8
DYAZIDE	8
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Eplerenone	8
Ethacrynic Acid	8
Furosemide	**8**
Hydralazine	8
Hydrochlorothiazide	**8**
HYGROTON	8
Hypertension	8
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prognosis than HFREF.
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ONLINE RxFILES EXTRAS

CI: DIURETICS: symptomatic gout, allergy sulpha: cross reactivity not proven, anuria, hyponatremia. β-BLOCKERS: asthma, 2nd or 3rd degree heart block, severe bradycardia, uncompensated HF, severe PAD. ACEI / ARB: bilateral artery stenosis (or kidney solitary stenosis if only 1 kidney), angioedema hx, (ACEI/ARB + aliskiren) diabetes, pre-contrast concern coronary angio, pregnancy (2nd & 3rd trimester; ? 1st trimester – appears safe). Less effective/safe in black people? CCB: systolic BP<90, recent MI with pulmonary edema Non-LA-DHP, sick sinus sx or 2nd/3rd degree AV block, systolic dysfx/HF especially diltiazem & verapamil.

Aliskiren RASILEZ✗ ⊗150,300mg tab daily $55; RASILEZ-HCTZ✗ ⊗ 150,300//12.5,25mg tab. Direct renin inhibitor (DRI) AE: diarrhea, HA, ↑K+, rash, allergy & pharyngitis.Rare: cough ~1%, angioedema, gout 0.2%. (rats: colonic mucosal hyperplasia). CI: Pregnancy. DI: cyclosporine, furosemide, grapefruit juice, irbesartan, juices, keto- & itra -conazole, + ACEi or ARB(↑CV events ALTITUDE; prehypertension NS AQUARIUS). High-fat meals reduce absorption.

	Generic/ TRADE / Strength	Comments/ Drug Interactions [11] DI	Adverse Events [8,10] AE	Indications ✓, Contraindication CI	Initial Dose (Max)	Usual Dose; $🇨🇦/30d
OTHER	**CloNIDine** CATAPRES, g 0.1ˢ, 0.2ˢ mg tab; (0.025mg tab) ▼	**CENTRAL ALPHA AGONIST** (3rd line): use if others CI/ refractory HTN **Clonidine**: •Used for acute ↓BP •DI: cyclosporine,mirtazapine,TCA's **Methyldopa**: • DI: levodopa↓BP,TCAs↑BP	•**Sedation,dry mouth**,↓HR,depression & **rebound HTN** on withdrawal,impotence	•On the Beers Criteria for older patients list •CI:HF/heart block,diabetes autonomic neuropathy	0.1mg BID (0.2mg TID)	0.1-0.2mg BID $19-27
	Methyldopa ALDOMET, g 125, 250, 500mg tab		•Sedation, dry mouth, impotence, depression, **hepatotoxic**, lupus like sx & ↓ platelets/RBC	•Used in pregnancy; •An option for pheochromocytoma	125mg BID (500mg QID)	250mg BID $21
	Prazosin MINIPRESS, g 1ˢ, 2ˢ, 5ˢ mg tab	**ALPHA BLOCKERS** (3rd line): use if others CI / refractory HTN **Doxoazosin** • removed from ALLHAT due to ↑ **HF/stroke** •**First dose syncope**: minimize by gradual dose titration & give @HS	•Sedation, dizziness, vertigo,headache, palpitations, ↑HR, fluid retention, weakness, nasal congestion & priapism.	•Useful for lower urinary tract symptoms (LUTS) e.g. poor stream, hesitancy, dribbling, incomplete voiding, prostatism [8,19] •An option for pheochromocytoma	0.5mg BID (5mg TID)	2mg BID $34
	Terazosin HYTRIN, g 1,2,5,10mg tab				1mg HS (10mg BID)	5mg HS $21
	Doxazosin CARDURA, g 1,2ˢ,4ˢmg tab				1mg HS (16mg daily)	4mg HS $28
	HydrALAZINE APRESOLINE, g 10ˢ, 25, 50mg tab	**VASODILATOR** •Reflex ↑HR, edema&renin sx activation; often add β-blocker/diuretic	•↑↑HR, aggravate angina,headache,dizzy, fluid retention,lupus like>200mg/d & hepatitis	•**Alt:** HFrEF hydralazine with isosorbide A-HeFT •**CI:** LVH. •IV 1st line HTN emergency in pregnancy	10mg QID (50mg QID)	25mg QID $18
	Labetalol TRANDATE, g 100ˢ, 200ˢ mg tab	**ALPHA & BETA BLOCKADE** •↓ BP more than other β-blockers	•Postural hypotension & **hepatotoxicity** more than other Beta-Blockers 7	•Used in pregnancy; •**CI:** as per β-Blockers above	100mg BID (400mg TID)	200mg BID $44

ACCUPRIL	9
ACE Inhibitor	9
Acebutolol	9
ADALAT	9
ALDACTONE	9
Aliskiren	9
ALTACE	9
Amlodipine	9
Angina	9
Antihypertensive	9
ARB	9
ATACAND	9
Atenolol	**9**
AVALIDE	9
AVAPRO	9
Azilsartan	9
Benazepril	9
BETALOC	9
Bisoprolol	9
BLOCADREN	9
Blood Pressure	**9**
BREVIBLOC	9
BYSTOLIC	9
Candesartan	9
CAPOTEN	9
Captopril	9
CARDIZEM	9
Carvedilol	9
Chlorthalidone	9
Cilazapril	9
COREG	9
CORGARD	9
Coronary Artery Disease	9
COVERSYL / PLUS	9
COZAAR	9
Diltiazem	9
DIOVAN	9
Diuretic	9
DYAZIDE	9
EDARBI	9
EDARBYCLOR	9

Enalapril	9
Eprosartan	9
Esmolol	9
Felodipine	9
Fosinopril	9
Hydrochlorothiazide	9
HYDRODIURIL	9
HYGROTON	9
Hypertension	**9**
HYZAAR	9
Indapamide	9
INDERAL	9
INHIBACE	9
Irbesartan	9
ISA	9
ISOPTIN	9
Labetalol	9
Lisinopril	9
LOPRESOR	9
Losartan	9
LOTENSIN	9
LOZIDE	9
MAVIK	9
Metoprolol	9
MICARDIS	9
MONITAN	9
MONOCOR	9
MONOPRIL	9
Nadolol	9
Nebivolol	9
Nifedipine	9
NORVASC	9
Olmesartan	9
OLMETEC	9
Oxprenolol	9
PAD	9
Perindopril +/- Indapamide	9
Pindolol	9
PLENDIL	9
PRINIVIL	9
PRINZIDE	9
Propranolol	9
Quinapril	9
Ramipril	**9**
RASILEZ	9
Raynaud's	9
RENEDIL	9
SECTRAL	9
SOTACOR	9
Sotalol	9
Spironolactone	9
TARKA	9
TEKTURNA	9
Telmisartan	9
TENORETIC	9
TENORMIN	9
TEVETEN	9
TIAZAC	9
Timolol	9
TRANDATE	9
Trandolapril	9
TRASICOR	9
TWYNSTA	9
Valsartan	9
VASERETIC	9
VASOTEC	9

Verapamil	9
VISKAZIDE	9
VISKEN	9
ZESTORETIC	9
ZESTRIL	9
Blood Pressure	**10**
CKD	10
Diabetes	10
Heart Failure	10
Hypertension	**10**
Isolated Systolic Hypertension	10
Left Ventricular Hypertrophy	**10**
LVH	**10**
Resistant Hypertension	10
Antihypertensive	10

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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).

Health Canada Jan/17 is advising Canadians that it has seized the unauthorized health product "**Blow**", by Limitless Pharma, from Atomik Nutrition at 450 Boulevard de Mortagne, Boucherville, QC. "Blow" is promoted as a pre-workout supplement and is labelled to contain the unauthorized drug 1,3 Dimethylamylamine (DMAA), which may pose serious health risks such as high blood pressure and stroke.

Health Canada Jul/18: Several drugs containing the ingredient **valsartan are being recalled by their manufacturers**. An impurity, **N-nitrosodimethylamine (NDMA), was found in the valsartan** used in these products. NDMA is a **potential human carcinogen**.

Health Canada Jan/19: has completed a safety review of **hydrochlorothiazide** and has found that prolonged use of the drug **could increase a person's risk for non-melanoma skin cancer**.

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RxFILES ONLINE EXTRAS: ORAL ANTIPLATELET & ANTITHROMBOTIC AGENTS

GENERIC/TRADE, g =generic	MECHANISM OF ACTION / INDICATIONS	ADVERSE EFFECTS	COMMENTS/CONTRAINDICATIONS (CI) / MONITOR (M) / DRUG INTERACTIONS (DI)	DOSE $ /30 DAY
DISCONTINUED ORAL ANTIPLATELETS				
Ticlopidine TICLID,g 250mg tab	PL **MOA**: irreversibly inhibits ADP platelet receptor P2Y12; proD 2-14% pts ↓↓2C19 **Indication:** 1° & 2° stroke prevention, CAD, post-intracoronary stent.	Diarrhea 20% → severe 6% TASS,GI upset 10% Rash 12% → severe 3% TASS, ↑ LFTs, Neutropenia 2.4% WBC <1.2, aplastic anemia, TTP: >1/5000, ~3-4 wks, seldom relapses	**CI:** allergy, bleeding disorders **DI**: is a 2C19 inhibitor **Comments:** not recommended due to SE CHEST'12 **M**: CBC q2wks x 3 mos →catch neutropenia/TTP; LFT **Landmark Trials:** see AAASPS, CLASSICS (see RxFiles On-Line Extras)	250mg po BID $80 CATS, TASS, AAASPS

Landmark Trials	Intervention	Population	Contribution to Current Knowledge
TRILOGY 868	ASA + Clopidogrel vs Prasugrel **EFFIENT**	NSTEMI (n=7243)	NS for primary outcome (CV death, recurrent MI, stroke) and for bleeding
TRITON-TIMI 38	ASA + Clopidogrel vs Prasugrel **EFFIENT**	High-risk ACS with PCI	Prasugrel ↓ risk of CV death/MI/stroke but ↑ risk of bleeds (major, life-threatening, CABG)
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 (±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.
rial	Intervention	Population	Contribution to Current Knowledge
ACTIVE-A, -W	See RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf		AF, A:ASA+clop vs ASA, n=7554; W:ASA+clop vs warf n=6706
ARCTIC	After 1yr of DAPT in DES pts, pts randomized n=1259 to ASA **or** ASA+clopidogrel/prasugrel, death/MI/stent thrombosis/stroke/revasc was 4% in each arm over ~17mons		
ARISTOTLE	See RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/ARISTOTLE-AF-Apixaban.pdf		apixaban 2.5-5mg BID vs warfarin, AF, n=18201, ~2yr
RELY 398	See RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/RE-LY-Trial-Dabigatran.pdf		dabi 150mg po BID vs dabi 110mg po BID vs warf, AF, n=18,113, 2yr
ROCKET-AF 623	See RxFiles Trial Summary: http://www.rxfiles.ca/rxfiles/uploads/documents/ROCKET-AF-Rivaroxaban.pdf		rivaroxaban 15-20mg vs warf, AF, n=14,264, ~2yr
WARIS-II 20 4 yrs, n=3,630	Warfarin INR 2.8-4.2, vs Warfarin INR 2-2.5 + ASA 75mg vs ASA 160mg po daily	Acute MI	Warfarin ± ASA most effective but ↑ non-fatal major bleed NNH=250/yr
WOEST 1yr, n=573	Clopidogrel with warfarin **± ASA** (open label)	PCI 941	Clopidogrel + warfarin **without ASA**: ↓bleeding 19vs44% & no increase in thrombotic events.
DAPT 1252 n=9961	ASA 75-162mg OD, + 12 or 30month of DAPT	DAPT Clop/pras after DES	DAPT 30month vs 1yr Stent thrombosis 0.4 vs 1.4%;MI/Stroke/death 4.3 vs 5.9%; but mod-sev bleed 2.5 vs 1.6%, & death 2 vs 1.5%.
PLATO n=18,000	ASA + Clopidogrel vs Ticagrelor **BRILINTA**	ACS→PCI,CABG or meds	Ticagrelor ↓ risk of CV death/MI/stroke but ↑ risk of fatal intracranial & non-CABG bleeds
MATCH 48 1.5 yrs, n=7,599	Clopidogrel PLAVIX 75mg po daily ± ASA 75mg po daily	Hx of stroke/TIA on PLAVIX	Ischemic events: combo 15.7 vs 16.7% alone NS. Bleeding: combo 2.6 vs 1.3% NNH=77 (?use combo for only first 21 daysAHA/ASA'18). Clopidogrel & ASA x3wk better than ASA for TIA, especially in subgroup who were not carriers of the CYP2C19 loss-of–function alleles. Chance 993 Clopidogrel & ASA x3mon better than ASA for TIA 5 vs 6.5%, but ↑ major bleeding 0.9 vs 0.4% . Point 2057
ESPS-2 6	AGGRENOX po BID vs Dipyridamole vs ASA alone x 2 years	N=6,602 history of ischemic stroke / TIA	Dipyridamole + ASA more effective than ASA alone for secondary stroke/TIA prevention. NNT=37/2 yrs to prevent 1 stroke/death.

RISK FACTORS

BLEEDING: Age >75, DM, elevated INR warfarin, female, ↓ Hct, HF/MI, ↑HR, length of antithrombotic tx, liver dx, ↑↓ systolic BP, medications (e.g. anticoagulants, antiplatelets, NSAIDs), previous GI bleed or stroke noncardioembolic, ↑SCr, ↓ wt. **Antithrombotic combination therapy:** e.g. warfarin ~4%/yr + ASA ~7%/yr or clopidogrel ~14%/yr; combination of all 3 ~16%/yr RR ↑4.6. 289, 418 **HAS-BLED ≥ 3** 466 www.crusadebleedingscore.org

STENT THROMBOSIS: DM, STEMI/ACS, prior stent thrombosis, ↓EF, ↓renal fx; lesion: bifurcation, longer stent, residual dissection, small stent diameter.

STROKE: **Modifiable:** EtOH, AF, DM,↑cholesterol, diet ↑fat + salt, ↓exercise **HTN**,LVH, obesity, metabolic syndrome, **smoking**. **Non-modifiable:** male,age, race, personal or family hx of TIA/stroke. **TIA/Stroke Risk Scores**: **Atrial Fib**:169 CCS'10, AHA'11 Overall stroke risk ~4.5%/yr. Warfarin vs ASA: 1°prevention 2x more effective, 3x more in 2° prevention.37 **$CHADS_2$** (http://www.vhpharmsci.com/sparc/). High risk: 4-18%/yr, prior stroke/TIA, systemic embolus, mitral stenosis, prosthetic valve. **$CHADS_2$ ≥2**. Tx: warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban: ↓RR 60%. Moderate risk: ~3%/yr, >75yrs, DM, HF, HTN. **$CHADS_2$ =1** (calculate the CHA_2DS_2VASc). Tx: warf, dabi, apix, riva or edox; or ASA+clopidogrel, ASA alone. Low risk: <2%/yr, 60-74yrs & no other risk factors. **$CHADS_2$ =0**. Tx: ASA alone ↓RR 25%, <60yrs ? no tx. **ABCD** estimates risk of stroke post-TIA. Score of 6→30% risk of stroke in next 7 days Rothwell 80,81,82 CT imaging also useful. **$ABCD^2$** → risk in 2,7 & 90 d of TIA. High risk if ≥4. Also used **ABCD3-I**. **RRE-90** : risk of 2° stroke. 415; QStroke
Risk of CV/stroke post TIA: 6.4% in first yr & 6.4% in second through fifth yrs. TIAregistry'18

VTE: Acute medical illness (infection, cardiac or respiratory failure), >60 yrs, central venous catheterization, ↑ D-dimer, immobility, IBD, malignancy/cancer tx (hormonal, chemo or radiation), major surgery or trauma to lower extremity, **meds** (? AP-A, OCP ? hold 4wks before elective surgery, erythropoiesis-stimulating agents, heparin HIT, HRT, ponatinib, raloxifene, steroids, tamoxifen, thalidomide …), myeloproliferative dx, nephritic syndrome, BMI ≥30kg/m², paroxysmal nocturnal hemoglobinuria, PICCs > CVCs, pregnancy & postpartum, previous VTE, rheumatoid arthritis, smoking, thrombophilia, varicose veins & long haul travel.

TRIAL	DESIGN	INTERVENTION	BENEFIT	HARM	COMMENTS
PERIPHERAL ARTERY DISEASE					
VOYAGER PAD (2020)	Double-blind randomized placebo-controlled international trial with ITT for efficacy (on-treatment analysis for safety) **POPULATION** N=6564 PAD + lower extremity revascularization (≤10 days) who were ≥50 years of age - mean age: 67 years - 26% female - 96% claudication - media ABI 0.56 - 65% endovascular procedure - 35% surgical - 23% critical limb ischemia - 51% on clopidogrel (up to 6 months allowed, at the discretion of the investigator)	Rivaroxaban 2.5mg po BID + ASA 100mg daily vs ASA 100mg daily alone Median duration of follow-up: 28 months (2.3 years)	Primary Endpoint: **Acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or CV death:** 15.5% (508/3286) vs 17.8% (584/3278), HR 0.85 (95% CI 0.76-0.96), p=0.009, ARR 2.3%, NNT 44 / 28 months Secondary Endpoints: **Acute limb ischemia:** 4.7% vs 6.9%, ARR 2.2%, NNT 46 / 28 months **Major amputation for vascular causes:** NS **MI:** NS **Ischemic stroke:** NS **CV death:** NS **All-cause mortality:** NS	Principle Safety Endpoint: **TIMI Major Bleeding:** NS Secondary Safety Endpoints: **ISTH Major Bleeding:** 4.3% (140/3256) vs 3.1% (100/3248), HR 1.42 (95% CI 1.10-1.84), p=0.007, ARI 1.2%, NNH 84 / 28 months **BARC Major Bleeding:** NS **Intracranial Bleeding:** NS **Fatal Bleeding:** NS **Discontinuation rates:** 33.2% vs 31.1% **Serious Adverse Events:** 29% (948 / 3256) vs 28.5% (927 / 3248)	**Compared to ASA alone, rivaroxaban 2.5mg BID + ASA 100mg daily:** - ↓ the risk of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke or CV death ARR 2.3%, NNT 44 / 28 months - ↑ the risk of ISTH major bleeding ARI 1.2%, NNH 84 / 28 months

LANDMARK TRIAL	INTERVENTION	POPULATION	CONTRIBUTION TO CURRENT KNOWLEDGE
PERIPHERAL ARTERY DISEASE			
VOYAGER PAD (2020)	Rivaroxaban 2.5mg po BID + ASA 100mg daily vs ASA 100mg daily alone x 28 months	**PAD + lower extremity revascularization** (≤10 days) who were ≥50 years of age (N=6564); 51% on clopidogrel	**Compared to ASA alone, rivaroxaban 2.5mg BID + ASA 100mg daily:** - ↓ the risk of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke or CV death: 15.5% (508/3286) vs 17.8% (584/3278), HR 0.85 (95% CI 0.76-0.96), p=0.009, ARR 2.3%, NNT 44 / 28 months - ↑ the risk of ISTH major bleeding: 4.3% (140/3256) vs 3.1% (100/3248), HR 1.42 (95% CI 1.10-1.84), p=0.007, ARI 1.2%, NNH 84 / 28 months
WAVE (2007)	Warfarin (INR 2-3, TTR 62%) + antiplatelet vs antiplatelet alone (92% ASA 81mg – 325mg) x 35 months	**PAD** (N=2161)	**Compared to antiplatelet alone, warfarin + antiplatelet:** - did not reduce the risk of MACE (NS) - ↑ the risk of life-threatening bleeding: 4% (43/1080) vs 1.2% (13/1081), RR 3.41 (95% CI 1.84-6.35), ARI 2.8%, NNH 36 / 35 months
MYOCARDIAL INFARCTION AFTER NON-CARDIAC SURGERY			
MANAGE (2018)	Dabigatran 110mg BID vs placebo x 16 months	**Myocardial *injury* within 35 days after non-cardiac surgery** (N=1754); 80% isolated ischemic troponin elevation, peak 82ng/L, 58% on ASA (~4% on a $P2Y_{12}$ inhibitor), ~45% discontinued their assigned study	**Compared to placebo, dabigatran:** - ↓ the risk of vascular mortality, non-fatal MI, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic VTE): 97/877 (11%) vs 133/877 (15%), HR 0.72 (95% CI

		drug ? does dabigatran ↑ the risk of MI in NVAF (see RxFiles Q&A); individuals with AF excluded from **MANAGE**	0.55-0.93), p=0.0115, ARR 4%, NNT 25 / 16 months - did not ↑ the risk of life-threatening, major, & critical organ bleeding (NS)
MECHANICAL HEART VALVES			
RE-ALIGN (2013)	Dabigatran 150mg, 220mg, or 300mg BID (based on kidney function, and then trough plasma levels) vs warfarin (INR 2-3 or 2.5-3.5)	Aortic- or mitral-valve replacement within the past 7 days, and those who had undergone such replacement at least 3 months earlier Phase 2 dose-validation study	- the study was stopped early (N=252) due to an excess of thromboembolic and bleeding events in the dabigatran group
Non-Cardioembolic Ischemic Stroke			
THALES (2020)	Ticagrelor LD 180mg x 1, then 90mg BID **+** ASA LD 300-325mg x 1, then 75-100mg daily vs ASA alone x 30 days	**Mild-to-moderate acute non-cardioembolic ischemic stroke** (NIHSS score ≤5; 91%) or high-risk TIA (ABCD^2 score ≥6) or symptomatic intracranial or extracranial arterial stenosis (≥50% narrowing) without thrombolysis or thrombectomy (N=11,016); 0.2% from North America, ~60% NIHSS score ≤3	**Compared to ASA alone, ticagrelor + ASA:** - ↓ the risk of stroke or death within 30 days: 5.5% (303/5523) vs 6.6% (362/5493), HR 0.83 (95% CI 0.71-0.96), p=0.02, ARR 1.1%, NNT 91/30 days (driven by ↓ in stroke as death NS) - did not reduce overall disability (modified Rankin scale, NS) - ↑ the risk of severe GUSTO bleeding: 0.5% (28/5523) vs 0.1% (7/5493), HR 3.99 (95% CI 1.74-9.14), p=0.001, ARI 0.4%, NNH 250 / 30 days - ↑ the risk of premature permanent discontinuation due to bleeding: 2.8% (152/5523) vs 0.6% (32/5493), HR 4.80 (95% CI 3.28-7.02), p<0.001, ARI 2.2%, NNH 46 / 30 days
SOCRATES (2016)	Ticagrelor (Day 1: LD 180mg, Day 2-90: 90mg BID) vs ASA (Day 1: 300mg, Day 2-90: 100mg daily)	Non-severe acute non-cardioembolic ischemic stroke or high-risk TIA without thrombolysis (N=13,199)	**Compared to ASA, ticagrelor:** - did not reduce the risk of stroke, MI, or death at 90 days
Embolic Stroke of Undetermined Source (ESUS)			
RE-SPECT ESUS (2016)	Dabigatran 150mg BID or 110mg BID vs ASA 100mg daily x 19 months	Embolic stroke of undetermined sources (N=5,390)	Compared to ASA, dabigatran was not superior for reducing recurrent stroke
NAVIGATE ESUS (2018)	Rivaroxaban 15mg daily vs ASA 100mg daily x 11 months	Embolic stroke of undetermined sources (N=7,213)	Terminated early due to lack of benefit & increased risk of bleeding with rivaroxaban

AGGRENOX	15
Antiplatelet	15
ASA	**15**
ASPIRIN	**15**
BRILINTA	15
Clopidogrel	**15**
Dipyridamole + ASA	15
PLAVIX	**15**
Ticagrelor	15
Anticoagulant	16
Antithrombotic	16
Apixaban	**16**
Betrixaban	16
BEVYXXA	16

COUMADIN	**16**
Dabigatran	**16**
DOACs	16
Edoxaban	**16**
ELIQUIS	**16**
LIXIANA	**16**
PRADAXA	**16**
Rivaroxaban	**16**
Warfarin	**16**
XARELTO	**16**
EFFIENT	**15**
Prasugrel	**15**

ORAL ANTIPLATELET & ANTITHROMBOTIC AGENTS

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women are at an increased risk of fetal loss. Moderate-intensity anticoagulation with warfarin (target international normalized ratio (INR) = 2.0 - 3.0) prevents recurrent venous thrombosis. The optimal management of other thrombotic aspects of patients with antiphospholipid antibodies remains uncertain. (LOE = 1a-))
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Ruiz-Irastorza Guillermo, Crowther Mark, Branch Ware, et al. **Antiphospholipid syndrome**, The Lancet, In Press, Corrected Proof, Available online 6 September 2010, ISSN 0140-6736, DOI: 10.1016/S0140-6736(10)60709-X.

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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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antiplatelet therapy is associated with an approximately 7% major bleeding risk. Thus, novel regimens are needed to reduce the bleeding risk.
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warfarin therapy (95% confidence interval 1.4-17.8, p=0.012). Warfarin was an independent predictor of major bleeding after PCI in patients receiving dual antiplatelet therapy. Prospective data to further characterize the safety of concomitant warfarin and dual antiplatelet therapy after PCI are needed.

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RxFiles Duration of DAPT, Dual & TT Online Extras:

COMPLETE LIST OF ABBREVIATIONS

☎ = EDS in SK ⊗=not covered by NIHB 2˚=secondary **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)

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

- The Canadian Cardiovascular Society 2018 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. WR/LQ
- 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 600mg 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)
  - Omit loading dose, initiate ticagrelor at time of next scheduled prasugrel dose

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

RxFiles Duration of DAPT, Dual & TT Online Extras:

RISK FACTORS FOR THROMBOTIC EVENTS AND BLEEDING

THROMBOTIC CV RISK FACTORS / HIGH-RISK FEATURES

- ACS (STEMI, NSTEMI, UA)
- CKD (CrCl <60mL/min)
- Complex lesions (bifurcation treated with 2 stents, stenting of chronic occlusion)
- Current smoker
- DM treated with medications
- Multiple stents (≥3 stents, ≥3 lesions) or use of biodegradable vascular scaffold
- Multi-vessel PCI / disease
- Long lesion length (>60mm)
- Left main or proximal LAD stenting
- Previous stent thrombosis
- Prior MI or troponin-positive ACS

BLEEDING RISK FACTORS

- Abnormal liver function
- Advanced age: >65 years old
- Anemia with hemoglobin <110g/dL
- CKD (CrCl <60mL/min)
- Excess alcohol consumption
- Frailty
- Hospitalized for bleeding within last year
- Hypertension
- Labile INR (time in therapeutic range <60%)
- Low body weight: <60kg
- Taking an OAC or antiplatelet
- Prior stroke / intracranial bleed
- Taking NSAIDs or prednisone regularly

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

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 (see below) 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** (see below) 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.

RxFiles Duration of DAPT, Dual & TT Online Extras:

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	

- **POPular Genetics**: Genotype-guided $P2Y_{12}$ inhibitor therapy was non-inferior to standard DAPT x 1 year for net adverse clinical events (NNT=125), & ↓ the bleed risk (NNT=37, driven by minor)

DAPT: CEREBROVASCULAR INDICATIONS			
Indication	**Antiplatelet Options & Maintenance Doses**	**Duration of DAPT**	**Comments**
Cardioembolic Stroke in AF OAC preferred over DAPT	ASA 75-325mg po daily + Clopidogrel 75mg po daily Note: - Prasugrel **CI** in patients with a history of stroke/TIA TRITON - Ticagrelor: NS vs ASA SOCRATES - 3 vs 2 antiplatelets (ASA, clopidogrel, dipyridamole): TIA/ stroke NS, ↑ bleeds TARDIS	lifelong	- DAPT may be considered if $CHADS_2$ or CHA_2DS_2VASc score <2 or unable to take OAC. See RxFiles AF Chart Pg 22. - **ACTIVE-W**: DAPT vs warfarin x 1.3 years, NNH=47 for stroke/non-CNS embolus/vascular death & NNH=37 minor bleeds.
Intracranial Artery Stenosis (Secondary Prevention)		90 days	- Indicated for severe stenosis (70-99%) of a major intracranial artery. CSBPR 2017 (B), AHA/ASA 2014 (IIb,B) - **SAMMPRIS**: DAPT x 90 days ± stent, then ASA 81-325mg daily. DAPT was started within 30 days of stroke/TIA.
Non-Cardioembolic Stroke (Secondary Prevention)		21 days CHANCE to 90 days POINT	- If started ≤ 24hr of minor ischemic stroke/TIA, may consider DAPT x 21 days, CSBPR'17 (B), AHA/ASA'18 (IIa,B-R), CHANCE then single antiplatelet (agent depends on if the patient was on an antiplatelet prior to their event, & if yes, which one) - **CHANCE** (China): DAPT vs ASA x 21 days, then clopidogrel vs ASA to Day 90; ↓ risk of stroke NNT 29, bleeding NS. - **POINT** 2018: DAPT vs ASA x 90 days; ↓ ischemic stroke NNT 67, ↑major bleeds NNH 200. Greatest benefit 1st 7 & 30 days. - Avoid DAPT >90 days: CSBPR'17 (A), AHA/ASA'14 (IIIA) **MATCH** (DAPT vs clopidogrel x 18 mos): DAPT no benefit; ↑ bleed risk >90 days (e.g.life-threatening NNH=50).**SPS3**(DAPT vs ASA x 3.4yr): no benefit; ↑ all-cause mortality (NNH=44) & major bleed risk (NNH=32).

RxFiles Duration of DAPT, Dual & TT Online Extras:

SUMMARY OF ISCHEMIC STROKE DAPT TRIALS (NON-CARDIOEMBOLIC): SECONDARY PREVENTION					
Study	**Regimen ***	**Start of Treatment in Relation to Event**	**DAPT Duration**	**Benefit**	**Harm**
POINT (2018)	- DAPT vs ASA 50-325mg (62% on ASA 81mg daily)	Randomized within 12 hours, 1st dose given ASAP	90 days	- ↓ risk of ischemic stroke, MI or death from ischemic vascular cause NNT=67 (↓ driven by ischemic stroke) - Benefit was greater in the 1st 7 days (p=0.04), & 1st 30 days (p=0.02), versus at 90 days	- ↑ risk of major bleeding NNH=200 - The risk of bleeding between the two treatment arms was not statistically significant during the first 7 days (p=0.34), versus Day 8-90 (p=0.04)
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

Apixaban	17
ASA	17
ASPIRIN	17
Bare-metal stents- BM	17
BRILINTA	17
Clopidogrel	17
COUMADIN	17
Dabigatran	17
DAPT	17
DOACs	17
Drug-eluting Stents-DES	17

Dual Antiplatelet Therapy	17
Dual Therapy	17
Edoxaban	17
EFFIENT	17
ELIQUIS	17
LIXIANA	17
NSTEACS	17
Peripheral Artery Disease	17
PLAVIX	17
PRADAXA	17
Prasugrel	17
Rivaroxaban	17
Stent Thrombosis	17
Ticagrelor	17
Warfarin	17
XARELTO	17
Apixaban	18
ASA	18
ASPIRIN	18
BRILINTA	18
Cardioembolic Stroke	18
Clopidogrel	18
COUMADIN	18
Dabigatran	18
DAPT	18
DOACs	18
Dual Therapy	18
Edoxaban	18
EFFIENT	18
ELIQUIS	18
Intracranial Artery Stenosis	18

LIXIANA	18
Non-Cardioembolic Stroke	18
PLAVIX	18
PRADAXA	18
Prasugrel	18
Rivaroxaban	18
Ticagrelor	18
Triple Therapy	18
Warfarin	18
XARELTO	18
Gastroprotection	**18**
Anticoagulant	**17**
Anticoagulant	**18**
Dual Antiplatelet Therapy	**18**

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DRUGS THAT ↑AF: [36] Antithrombotics (anagrelide, clopidogrel), CV (acetylcholine, adenosine, arbutamine, atenolol, digoxin, diltiazem, dobutamine, dopamine, dopexamine, flosequinan, isosorbide mononitrate, losartan, perflexane, perfluorbutane, thiazides, verapamil), Respiratory (ephedrine, methylprednisolone, phenylephrine, pseudoephedrine, salbutamol, terbutaline, theophylline), Cytostatics (5-fluorouracil, cisplatan, docetaxel, etoposide, gemcitabine, ibrutinib, ifosfamide, interferon-gamma, interleukin-3, interleukin-6, melphalan, profimer, verteporfin), CNS (apomorphine, atropine, bupivacaine, clozapine, donepezil, fluoxetine, physostigmine, sumatriptan, tranylcypromine, trazodone), Genitourinary (hexoprenalin, magnesium sulphate, sildenafil, terbutaline), Antiemetics (alizapride, benzquinamide), Miscellaneous (amphotericin B, amifostine, anabolic steroids, azathioprine, calcium, disulfiram, etanercept, etretinate, fluorescein, flupirtine, gallium nitrate, levocarnitine, lithium, nesiritide, niacin, nicotine, NSAIDs, pentagastrin, zalcitabine)

HERBALS THAT ↑AF: limited data; caffeine controversial, ginseng, guarine, ma Huang, yohimbine. **DI**: many herbals ↑ bleeding risk via platelets (e.g. garlic) or ↑INR or ↑ clotting risk via ↓INR; limited data with DOACS avoid combo until safety known. See Herbal DI CHT Pg 209.

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

Factors which ↑hemorrhagic risk:[1] renal impairment (CrCl <50mL/min), active ulcerative GI disease, age≥75yrs, ASA, bacterial endocarditis, brain/spinal/ophthalmic surgery, clopidogrel, congenital/acquired coagulation disorders, NSAID, P-gp inhibitors co-med (eg. amiodarone, azole [antifungals], clarithromycin, cyclosporine, diltiazem, erythromycin, HIV [Pts], quinidine, tacrolimus, tamoxifen, verapamil), recent: biopsy/major trauma/GI bleed/ intracranial hemorrhage, steroids & thrombocytopenia.

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. [37] (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.[38] (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.[39] (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[40] (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		

Thrombosis Canada: DIRECT ORAL ANTICOAGULANT (DOAC) MONITORING CHECKLIST:
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):[41]

- 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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Anticoagulation Colour Comparison Chart

This editorial synthesis was based on interpretation of data from RCTs (RELY, ROCKET-AF, ARISTOTLE, ENGAGE-AF), CADTH reports, product monographs & clinical consultation.

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Apixaban	22
Atrial Fibrillation	22
COUMADIN	22
Dabigratran	22
DOACs	22
Edoxaban	22
ELIQUIS	22
LIXIANA	22
PRADAXA	22
Rivaroxaban	22
Warfarin	22
XARELTO	22
Anticoagulant	22

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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 diagnose	HF very likely
Acute Care Setting				
BNP (pg/mL)	**All**	**<100**	**100-400**	**>400**
NT-proBNP (pg/mL)	**<50**	**<300**	**300-450**	**>450**
	50-75	**<300**	**450-900**	**>900**
	>75	**<300**	**900-1800**	**>1800**
Ambulatory Care Setting				
BNP (pg/mL)	**All**	**<50**		
NT-proBNP (pg/mL)	**All**	**<125**		

Heart Failure	**23**
ACE Inhibitor	24
ALDACTONE	**24**
ALTACE	**24**

ARB	24
ATACAND	24
Candesartan	24
CAPOTEN	24
Captopril	24
DIOVAN	24
Enalapril	24
ENTRESTO	24
Eplerenone	24
Heart Failure	24
INSPRA	24
Lisinopril	24
MAVIK	24
PRINIVIL	24
Ramipril	**24**
Sacubitril / Valsartan	24
Spironolactone	**24**
Trandolapril	24
Valsartan	24
VASOTEC	24
ZESTRIL	24
Beta-blocker	25
Bisoprolol	**25**
Carvedilol	25
COREG	25
Dapagliflozin	25
Digoxin	25
Empagliflozin	25
FORXIGA	25
Heart Failure	25
JARDIANCE	25
LANCORA	25
LANOXIN	25
LOPRESOR	25
Metoprolol	25
MONOCOR	25
TOLOXIN	25
ZEBETA	25
APRESOLINE	26
Bumetanide	26
BURINEX	26
Diuretic	26
EDECRIN	26
Ethacrynic acid	26
Furosemide	26

Heart Failure	26
Hydralazine	26
IMDUR	26
ISORDIL	26
Isosorbide	26
Ivabradine	26
LASIX	26
Metolazone	26
Vericiguat	26
VERQUVO	26
ZAROXOLYN	26

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FDA Aug/15 is alerting health care providers, patients, and caregivers about **serious adverse events associated with LVADs**. These adverse events include an increased rate of pump thrombosis (blood clots inside the pump) with Thoratec's HeartMate II and a high rate of stroke with the HeartWare HVAD since approval of the devices. FDA is also aware of bleeding complications related to

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New: **Lomitapide JUXTAPID** 5,10,20mg cap✗ ⊗; 40[-60]mg daily $375,000/yr for HoFH for adults, MTP Θ, **AE**: ↑LFTs & GI AE, ↑hepatic [fat]; **DI**: 3A4,P-gp. USA: **Mipomersen KYNAMRO** 200mg SC weekly $175,000/yr for HoFH age ≥12yrs, antisense mRNA [for ApoB], **AE**: ↑LFTs & GI [AE], inj site [rx], nausea, HA.
☎=EDS Sask. ✘ Non-formulary SK ✆=prior NIHB ⊗not covered NIHB ▼=covered NIHB ✓Indication/Use **AE**=adverse event **DI**=Drug Interaction **Dx**=disease **dysfx**=dysfunction **GI**=stomach **HDL**=high density lipoprotein **HMG** CoA reductase inhib→STATIN **LDL**=low density lipoprotein **NS**=non significant **TG**=triglyceride =↓dose renal dysfx.. FG=fasting glucose

Bempedoic Acid NEXLETOL for LDL-C lowering:

- MOA: Oral adenosine triphosphate-citrate lyase (ACL) inhibitor (i.e. reduces hepatic cholesterol synthesis)
- FDA approved for alone or fixed-dose combination with ezetimibe (Nexlizet) as an adjunct to diet & maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C
- LDL-C lowering: 15-17% when added to maximally tolerated statin, 36% when combined with ezetimibe + statin [CLEAR WISDOM, CLEAR HARMONY, CM, CLEAR SERENITY, CLEAR Tranquility]
- AE: back pain, extremity pain, elevated hepatic enzymes, hyperuricemia, gout, tendonitis, respiratory tract infection, muscle spasms, abdominal pain or discomfort, anemia, BPH. Rare: tendon rupture 0.5%
- DI: increases serum concentrations of simvastatin & pravastatin – limit doses to simvastatin 20mg & pravastatin 40mg to reduce risk of myopathy
- CV outcomes: unknown
- Dose: Bempedoic acid 180mg po once daily

ACC / AHA 2019 Primary Prevention

- Low risk (ASCVD <5%): emphasize lifestyle to reduce risk factors
- Borderline risk (ASCVD 5-7.4%): if risk estimate + risk enhancers favour statin, initiate moderate-intensity statin
- Intermediate risk (ASCVD risk 7.5-19%): if risk estimate + risk enhancers favour statin, initiate moderate-intensity statin to reduce LDL-C by 30-49%
- High risk (ASCVD risk ≥20%): initiate statin to reduced LDL-C ≥50%

AHA'18 [2]: **tx with statins** if **ASCVD,** Diabetes 40-75yr, high CV risk (≥7.5% CV 10yr risk) [USPSTF'16 ≥10%].
Consider **high** intensity statin (**ATO** 40-80mg, **ROS** 20-40mg) if ASCVD, LDL ≥4.9, ≥20% CV 10 yr risk; or **moderate** intensity statin (if ≥75yr **or** diabetes). Consider non-statin add-on if **↑risk ASCVD & LDL ≥1.8**.

2012 Canadian Cardiovascular Society- 10 year risk of Cardiovascular (CVD) disease (based on Framingham Heart Study)

American Cardiovascular Society- Framingham Risk Score (Printable version): https://www.ccs.ca/images/Guidelines/Tools_and_Calculators_En/FRS_eng_2017_fnl_greyscale.pdf

RISK*	MEN										WOMEN									
AGE	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+
Age points	0	2	5	7	8	10	11	12	14	15	0	2	4	5	7	8	9	10	11	12
TOTAL CHOL (mmol/l)																				
<4.1						0									0					
4.1-5.2						1									1					
5.2-6.2						2									3					
6.2-7.2						3									4					
> 7.2						4									5					
HDL (mmol/l)	<0.9		0.9-1.2		1.2-1.3	1.3-1.6			>1.6		<0.9		0.9-1.2		1.2-1.3		1.3-1.6		>1.6	
	+2		+1		0	-1			-2		+2		+1		0		-1		-2	
SYSTOLIC BP (mmHg)	Not Treated						Treated				Not Treated						Treated			
	<120			-2			<120			0	<120			-3			<120			-1
	120-129			0			120-129			2	120-129			0			120-129			2
	130-139			1			130-139			3	130-139			1			130-139			3
	140-159			2			140-159			4	140-149			2			140-149			5
	≥160			3			≥160			5	150-159			4			150-159			6
											>160			5			>160			7
SMOKER																				
No						0									0					
Yes						4									3					
Diabetic																				
No						0									0					
Yes						3									4					
TOTAL POINTS																				

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.

ALL patients with CAD, CVD, PAD; most with Diabetes [age >40 or >30 with 15 year history] of DM & chronic renal disease [GFR <30mL/min] are considered high risk, regardless of the risk score.

Cardiovascular Disease (CVD) Risk Asseessment Tools:

1) http://www.cvriskcalculator.com/ [AHA/ACC, 2013]
   - Considers: age, gender, race, total cholesterol, HDL cholesterol, SBP, DBP, treatment of hypertension, diabetes, smoking status
2) http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/ [ACC, 2018]
   - Considers: age, sex, race, SBP, DBP, total cholesterol, HDL, LDL, diabetes, smoking status, treatment of hypertension, use of statin, use of aspirin
3) http://www.myhealthcheckup.com [Canada]
   - Considers: age, gender, height, weight, waist measurement, total cholesterol, LDL, HDL, SBP, DBP, blood glucose; treatment of: hypertension, high cholesterol or diabetes; existence of: heart disease, stroke/TIA, PVD, family hx (CVD or diabetes), exercise, smoking status
4) https://www.projectbiglife.ca/cardiovascular-disease [Canada]

- Considers: age, sex, smoking (amount), alcohol consumption (amount), nutrition, physical activity, education level, weight, height, diabetes, hypertension

5) https://www.framinghamheartstudy.org/ [USA: 10year and 30year risk assessment available; interactive and excel spreadsheet]
   - Considers: age, sex, diabetes, smoking status, SBP, total cholesterol, HDL, BMI
6) http://chd.bestsciencemedicine.com/calc2.html [4 different calculators; data from USA, UK, New Zealand]
7) http://www.reynoldsriskscore.org/ [UK]
   - Considers: age, gender, BP, cholesterol, smoking status, hsCRP, family hx (MI)
8) http://www.jbs3risk.com/ [UK]
   - Considers: age, gender, ethnicity, BMI, townsend, total cholesterol, HDL, SBP

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**.

Historical notes: **Agents**: **↑↑LDL**⇨**HMG** +/- resin +/-ezetimibe; **↑↑LDL & ↑TG**⇨**HMG**; **↑↑LDL & ↓HDL**⇨**HMG** +/- fibrate/niacin; **Normal LDL & ↑↑TG**⇨fibrate/niacin/omega 3 fatty acid 22 or combo; **Normal LDL & ↓HDL**⇨fibrate/niacin or combo

Alirocumab	27
Atorvastatin	**27**
Bezafibrate	27
BEZALIP	27
CHOLESTAGEL	27
Cholesterol	27
Cholestyramine	27
Colesevelam	27
COLESTID	27
Colestipol	27
CRESTOR	27
Drug-Induced Hyperlipidemia	27
Dyslipidemia	27
Evolocumab	27
Ezetimibe	27
EZETROL	27
Fenofibrate	27
Fluvastatin	27
Gemfibrozil	27
Icosapent Ethyl	27
LESCOL	27
Lipid	27
LIPIDIL	27
LIPITOR	**27**
LOPID	27
Lovastatin	27
MEVACOR	27
NIACIN	27
NIASPAN	27
Nicotinic acid	27
OLESTYR	27
PRALUENT	27
PRAVACHOL	27
Pravastatin	27
REPATHA	27
Rhabdomyolysis	27
Rosuvastatin	27
Simvastatin	**27**
VASCEPA	27
WELCHOL	27
ZOCOR	**27**

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FDA Mar/10 notified healthcare professionals and patients that, based on review of data from a large clinical trial and other sources, there is an increased risk of **muscle injury** in patients taking the highest approved dose of the cholesterol-lowering medication, Zocor (**simvastatin**) **80 mg**, compared to patients taking lower doses of simvastatin and possibly other drugs in the "statin" class. Reviewing preliminary data from one clinical trial, the agency found that muscle injury, including rhabdomyolysis, was more common among patients on the 80-mg dose of simvastatin versus a 20-mg dose (0.9% vs. 0.02%). In addition, 11 (0.02%) of the patients in the simvastatin-80-mg group developed rhabdomyolysis compared with no patients in the simvastatin-20-mg group.

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

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

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

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

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Pfizer April/08 In a study in patients with mild-to-moderate Alzheimer's disease (AD), the addition of Lipitor (atorvastatin calcium tablets) 80 mg to Aricept® (donepezil HCl) 10 mg showed no significant differences in cognition or global function (key measures of Alzheimer's progression) compared to placebo plus Aricept 10 mg. Furthermore, no statistically significant differences were seen on various cognitive, behavioral and functional secondary endpoints. However, the Lipitor arm was not associated with greater cognitive decline than the placebo arm in this trial. The results were presented today at the annual American Academy of Neurology meeting in Chicago. The 18-month study, called Lipitor's Effect on Alzheimer's Dementia (**LEADe**), included 640 patients and is the largest statin study in Alzheimer's disease.
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RxFiles Post-MI On-Line Extras: Chart originally prepared with D Jorgenson PharmD; Updated by B Jensen BSP, L Regier BSP BA

CVD RISK Factors: [56,63] **Cholesterol:↑LDL** ApoB/ApoA1 ratio used in INTERHEART, low HDL ≤1; **Smoking**; **Diabetes**; ↑**BP** especially systolic; **Abdominal obesity**: **waist/hip ratio** (♂ ≥0.9; ♀ ≥0.85), BMI >25, Waist size [57] (♂ >102cm,40inch; ♀ >89cm,35inch), **stress** & **depression;**?migraine ♀ with aura; **lack** of **vegetables**, **fruits, exercise** (30-60mins ≥5-7x/week) **& alcohol** (0-2drinks/d ♂=14/week ♀=9/week); Family Hx of premature heart dx (Age: ♂ <55, ♀ <65) [61]; Microalbuminuria [61]; renal dysfx [58] & age (♂ >55, ♀ >65); cocaine abuse. Not moderate coffee intake. [63]Poorer prognosis if serum sodium <136 mEq/L.

colchicine vs placebo post-MI: **LoDoCo2** (N=5522) 0.5mg daily ↓ CV outcomes **NNT=35**, ↑myalgia **NNH=41**/29mon; **COLCOT** (N=4745) 0.5mg daily ↓ CV outcomes **NNH=63**/23 months.

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)

ACE Inhibitor	28
Acebutolol	28
ALDACTONE	28
ALTACE	28
ARB	28
ASA	28
ASPIRIN	28
ATACAND	28
Atenolol	**28**
Atorvastatin	28
Beta-blocker	28
Bisoprolol	**28**
BLOCADREN	28
BRILINTA	28
Candesartan	28
CAPOTEN	28
Captopril	28
Carvedilol	28
Clopidogrel	28
COREG	28
Coronary Stent	28
COVERSYL / PLUS	28
CRESTOR	28
DAPT	28
DIOVAN	28
EFFIENT	28
Enalapril	28
Eplerenone	28
INDERAL	28
INSPRA	28
LIPITOR	28
Lisinopril	28
LOPRESOR	28
MAVIK	28
Metoprolol	28
MONITAN	28
MONOCOR	28
MRA	28
Myocardial Infarction	28
Perindopril +/- Indapamide	28
PLAVIX	28
Prasugrel	28
PRAVACHOL	28
Pravastatin	28
Propranolol	28
Ramipril	28
Rosuvastatin	28
SECTRAL	28
Simvastatin	28

Spironolactone	28
Statin	28
STEMI	28
TENORMIN	28
Ticagrelor	28
Timolol	28
Trandolapril	28
Valsartan	28
VASOTEC	28
ZESTRIL	28
ZOCOR	28
Colchicine	28

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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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FDA Nov/13: warning health care professionals of the rare but serious risk of heart attack and death with use of the cardiac nuclear stress test agents **Lexiscan (regadenoson) and Adenoscan (adenosine).**
FDA Nov/17 is alerting the public, health care providers, lab personnel, and lab test developers that **biotin (Vitamin B7)** can significantly interfere with certain lab tests and cause incorrect test results which may go undetected. Biotin in blood or other samples taken from patients who are ingesting high levels of biotin in dietary supplements can cause clinically significant incorrect lab test results. The FDA has seen an increase in the number of reported adverse events, including one death, related to biotin interference with lab tests. Biotin in patient samples can cause falsely high or falsely low results, depending on the test. Incorrect test results may lead to inappropriate patient management or misdiagnosis. For example, a falsely low result for troponin, a clinically important biomarker to aid in the diagnosis of heart attacks, may lead to a missed diagnosis and potentially serious clinical implications. The FDA has received a report that one patient taking high levels of biotin died following falsely low troponin test results when a troponin test known to have biotin interference was used. The FDA is aware of people taking high levels of biotin that would interfere with lab tests. Many dietary supplements promoted for hair, skin, and nail benefits contain biotin levels up to 650 times the recommended daily intake of biotin. Physicians may also be recommending high levels of biotin for patients with certain conditions such as multiple sclerosis (MS). Biotin levels higher than the recommended daily allowance may cause interference with lab tests.
FDA Nov/19: is particularly concerned about **biotin interference causing a falsely low result for troponin**, a clinically important biomarker to aid in the diagnosis of heart attacks, which may lead to a missed diagnosis and potentially serious clinical implications.
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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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EMA May/19: The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has recommended **revoking marketing authorizations for fenspiride medicines because of heart risks** (eg. QT), preventing them from being sold in the European Union (EU).

FDA Feb/10 notified healthcare professionals and patients that it is reviewing clinical trial data about a potentially serious effect on the heart from the use of Invirase (saquinavir) in combination with Norvir (ritonavir), antiviral medications given together to treat HIV infection. The data suggest that together the two drugs may affect the electrical activity of the heart, known as prolonged QT or PR intervals.

FDA Nov/10 is requesting that manufacturers of the painkiller **propoxyphene** pull the drug from the market because of concerns over cardiotoxicity. (Propoxyphene is marketed alone as Darvon & combined with acetaminophen as Darvocet.) The agency's request is based on data showing that, even when taken at therapeutic doses, the drug can lead to potentially dangerous changes in the heart's electrical activity, including prolonged PR & QT intervals & widened QRS complex. FDA advises clinicians to stop prescribing propoxyphene and to ask current users to discontinue the drug. FDA's MedWatch alert

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

FDA July/11 FDA has added a warning to the label of the atypical antipsychotic quetiapine (Seroquel) cautioning about potential increases in the QT interval. Postmarketing cases of QT prolongation have been reported in some 17 patients, according to the *New York Times.* These patients had overdosed on quetiapine, had other illnesses, or were taking other medications that can cause electrolyte imbalance or QT prolongation.

FDA Aug/11 The antidepressant citalopram (marketed as Celexa) should not be prescribed at doses above 40 mg/day because higher dosages can cause arrhythmias, the FDA has warned.

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

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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Gupta A, Mody P, Pandey A. Inappropriate Antibiotic Therapy in a Patient With Heart Failure and Prolonged QT Interval: A Teachable Moment. JAMA Intern Med. 2015 Nov 1;175(11):1748-9. (**quetiapine & moxifloxacin**)

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.

Health Canada Aug/17: Health Canada concluded that a link could not be established between **desloratadine** use and the development of **abnormal heart rhythm**. However, Health Canada will continue to monitor the safety of desloratadine.

Health Canada Mar/18: **Sertraline-** caution should be exercised, because of concentration dependent prolongation of the QTc interval.

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MHRA Dec/11 **Citalopram and escitalopram** are associated with dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval. ECG measurements should be considered for patients with cardiac disease, and electrolyte disturbances should be corrected before starting treatment. For citalopram, new restrictions on the maximum daily doses now apply: 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment. For escitalopram, the maximum daily dose for patients older than 65 years is now reduced to 10 mg/day; other doses remain unchanged.

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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Online Extras for TOPICAL CORTICOSTEROIDS Comparison Chart:

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

Tx Escalator ⇧			
			Systemic treatment
			Phototherapy
		Wet dressings	Wet dressings
		Topical calcineurin inhibitors	Topical calcineurin inhibitors
	Low potency corticosteroids	Low potency corticosteroids	Low potency corticosteroids
	emollients	emollients	emollients
	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

Amcinonide	30
ARISTOCORT	30
Beclomethasone	30
BETADERM	30
Betamethasone Dipropionate	30
Betamethasone Glycol	30
Betamethasone Valerate	30
BETEFLAM	30
Calcipotriol	30
CELESTODERM-V, V/2	30
Clobetasol Propionate	30
Clobetasone Butyrate	30
CLOBEX	30
CORTODERM	30
Crisaborole	30
CUTIVATE	30
CYCLOCORT	30
DERMAFLEX	30
DERMA-SMOOTHE/FS	30
DERMATOP	30
DERMOVATE	30
DESOCORT	30
Desonide	30
DESOXI	30
Desoximetasone	30
Diflucortolone Valerate	30
DIPROLENE GLYCOL	30
DIPROSALIC	30
DIPROSONE	30
DOVOBET	30
ECTOSONE	30
ELIDEL	30
ELOCOM	30
EMO-CORT	30

Emollient	30
ENSTILAR	30
EUCRISA	30
EUMOVATE	30
Fluocinolone	30
Fluocinonide	30
FLUODERM	30
Halcinonide	30
Halobetasol Propionate	30
HALOG	30
HYDERM	30
Hydrocortisone	**30**
HYDROVAL	30
KENALOG (ORABASE)	30
LIDEMOL	30
LIDEX	30
LOTRIDEM	30
LUXIQ	30
LYDERM	30
Mometasone	30
NERISALIC	30
NERISONE	30
OLUX	30
ORACORT DENTAL	30
Pimecrolimus	30
PROPADERM	30
PROTOPIC	30
SPECTRO ECZEMA CARE	30
SYNALAR REG	30
Tacrolimus	30
TARO-SONE	30
Topical Corticosteroids	30
TOPICORT	30
TOPILENE GLYCOL	30
TOPISONE	30
TRIADERM	30
Triamcinolone	30
ULTRAVATE	30
UREMOL-HC	30
WESTCORT	30
XAMIOL	30
Corticosteroid	**30**
Steroid	**30**

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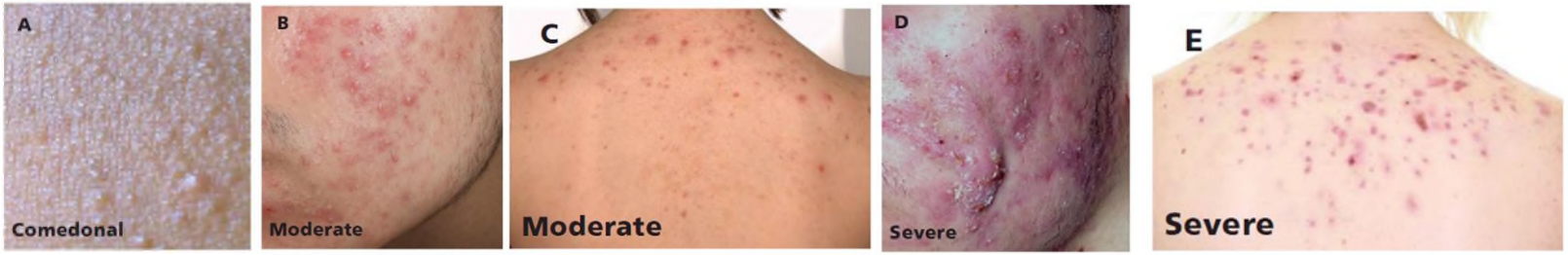
ACNE: Online Extras

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%	**Common:** less irritating than BPO, burning, stinging, pruritus & erythema **Serious**: rare systemic salicylate toxicity: nausea, vomiting, diarrhea, dizziness, loss of hearing, lethargy, psychic disturbances & hyperpnea ?protect from sun 8-12 weeks for noted improvement	✓ Used with topical retinoids to treat mild comedonal acne or 2nd line monotherapy agent[3] (also for seborrhea & psoriasis). **Not commonly recommended** (less potent than equal strength BPO). **D**: ↑ **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:

Name	Active Ingredient	Base
Adasept	BPO 5%	Gel
Clean & Clear Continuous Control	BPO 5%	Lotion; water based
Clean & Clear Persa-Gel	BPO 5%	Gel; water based
Clinique Acne Solutions Clearing Moisturizer	BPO 2.5%	Lotion
Life Acne Medication	BPO 5%	gel
Medicated Acne Gel	BPO 5%	Gel
Nature's Cure Acne Treatment	BPO 5%	Cream
Obagi Clenziderm Acne Lotion	BPO 5%	Lotion; water based

List of Benzoyl Peroxide Products (discontinued)
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 LOTION = BPO 5% lotion; 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)

Acne	31
ACZONE	31
Adapalene	31
ADASEPT	31
AKLIEF	31
Azelaic acid	31
BENZAC W	31
BENZACLIN	31
BENZAGEL	31
BENZAMYCIN	31
Benzoyl Peroxide	31
BIACNA	31

BPO	31
Cetaphil	31
CLEARASIL	31
Clindamycin	31
CLINDOXYL	31
Dapsone	31
DIFFERIN	31
Erythromycin	31
FINACEA	31
NEO-MEDROL Acne	31
NEUTROGENA	31
Olay	31
OXY	31
Pears	31
Petrophylic	31
PROACTIVE	31
RETIN-A	31
Soap	31
Spectro Gel	31
STIEVA-A	31
STIEVAMYCIN	31
SULFACET-R	31
TactuPump	31
Tazarotene	31
TAZORAC	31
Tea Tree Oil	31
Trifarotene	31
Vitamin A acid	31
ACCUTANE	32
Acne	32
ALDACTONE	32
ALESSE	32
AMZEEQ	32
CLARUS	32
DALACIN C	**31**
DIANE-35	32
DOXYCIN	32
Doxycycline	32
EPURIS	32
ERYC	32
Erythromycin	32
Isotretinoin	32
MINOCIN	32
Minocycline	32
PROLOPRIM	32
Spironolactone	32
Tetracycline	32
TETRACYN	32
Tretinoin	32
TRI-CYCLEN	32
YASMIN	32
YAZ	32

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Additional info:

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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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clindamycin and tretinoin approved for once daily use for the topical treatment of acne vulgaris in patients 12 years or older.
Nov 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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National Institute of Arthritis and Musculoskeletal and Skin Diseases www.niams.nih.gov/Health_Info/Acne/default.asp

Head Lice and Scabies Chart

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Warts

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Online Extras:

Wart therapies rarely used – but may consider in recalcitrant warts	
Intralesional Immunotherapy	Uses mumps, candida, or trichophyton skin test antigen preparations. Choose the agent that elicits greatest immune response in patient and inject intralesionally q3weeks. Minor fever, myalgia, and erythema may occur.[25]
Photodynamic Therapy	5-aminolavulinic acid (ALA) is applied topically to warts, where it is photoactivated with red 633-nm light-emitting diodes. When used at 2–3-week intervals, had a 68% improvement.[12]
Pulsed-dye Therapy	Intense heating of dilated/congested dermal vessels present in most warts. Low risk of adverse effects. Requires a smoke evacuator and PPE for HCPs doing procedure necessary since viral wart particles may aerosolize during the procedure and spread the infection.[39]
Trichloroacetic Acid	Corrosive agent; causes intense burning for 5-10 minutes after application.[11] Applied sparingly by healthcare professional directly onto wart surface with a wooden or cotton tipped applicator. Usually applied weekly or every 2 weeks.[94] Most suitable for small acuminate or popular warts, less easy to use on keratinized and large lesions. Excess application may cause scarring; it is a good idea to protect surrounding skin with petroleum jelly.[65] A neutralizing agent (**5% Na Bicarb**) should be readily available in case of spills. When used optimally, a shallow ulcer forms that heals without scarring. Clearance rates of 56-94% reported; recurrence rate of 36%. Safe in pregnancy.[35] Can be used for internal warts.[35] Cost $20 ✗ ⊗.

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used in this study. Overall cure rate was **86.9%** - 14/23 responding after 1 month, and in **20/23** after 2 months (complete resolution, no scarring, but minimal hypo- or hyperpigmentation). 100% of pts on zinc sulfate experienced nausea, 5 pts experienced vomiting (21.7%), and 3 pts had mild epigastric pain (13%). Itching – earliest symptom, mild to moderate itching was experienced by all pts whose warts resolved (100%), starting on average after 5 days of treatment. Itching persisted until warts disappeared.

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To debate:

-discourage sex with anogenital warts / encourage condom use / talk about harm reduction. Contact partners. STI testing. Podofilm note: Avoid sexual intercourse on days cream is applied.

-meat handlers: useful info or not? Currently in.

-what's the right dose of zinc to use – mega mega or just e.g. 200mg zinc gluconate

-imiquimod pregnancy: orange vs green.
-I sent trichloracetic acid to online extras – nice find.
-did Taylor get back to us on extra cold being better? I've adjusted the language a little to be less definitive.

Nikola:
For monitoring, I find it strange there is nothing to advise on. Is it common for secondary bacterial infections to develop? Do you treat for specified time frame regardless or how does one know when the wart is gone?

Debbie:
Can the titles in the table below be bigger font? There seems to be space. And can q2 weeks be spelled out?
SA, first mention – is there room to put Salicylic Acid (SA)?
In the reassess column, I am wondering about the "no effect" – unlikely someone is going to see no effect … perhaps …if lack of response after …
With the checks and x's below, one could put in a bit of a key for these pros and cons in the "Choose Therapy" title line. (Sometimes we use checks for indicated, and x's for not covered on SK formulary, so added key would avoid any mis-interpretation

I don't like to interpret a NNT without a time frame attached to it :)
See references.
This isn't obvious to me what more aggressive means? Compared to what? And same comment from before with NNT and timeframe.
I like the obvious pros /cons formatting here but it isn't carried out for the rest of the categories?
Unclear how to access this product (do you mean is it RX or not?)
I am totally going to show my ignorance here… what about valacyclovir?? Am I missing something? I thought people use it for tx and suppressions. (Maybe Debbie is thinking of shingles, herpes?)

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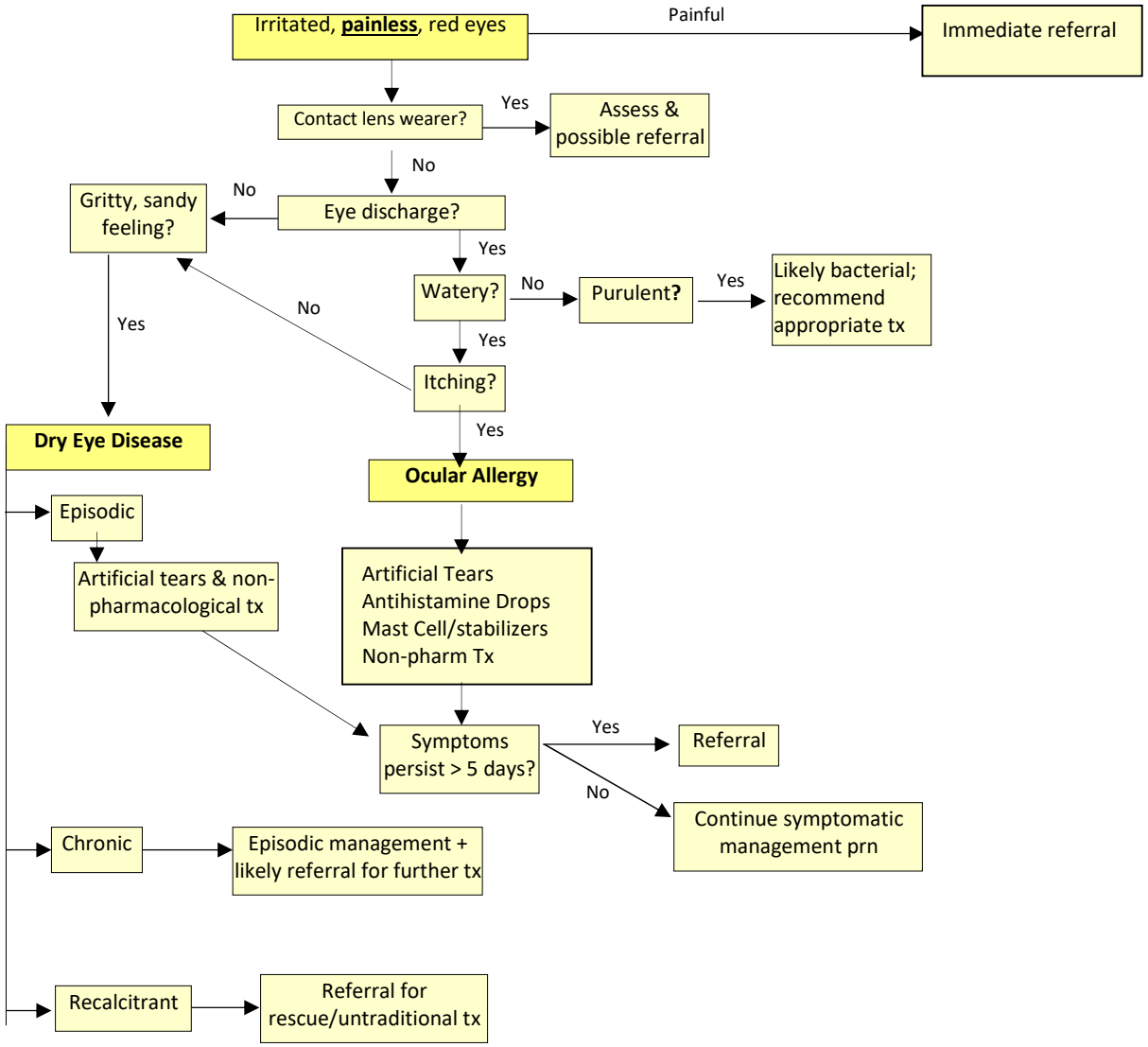
Patient Questionnaires for DED

- Ocular Surface Disease Index
- 5-item Dry Eye Questionnaire (DEQ-5)
- Standard Patient Evaluation of Eye Dryness (SPEED)

Treatment Algorithm for the **Painless**, irritated, red eye.



Artificial Tear Products (adapted from CTMA Ophthalmic Products: Ocular Lubricants Chart)
Products organized by ingredient, but may have varying concentrations

Product	Preservative	Contact Lens Compatible
Sodium carboxymethycellulose		
Refresh Celluvisc	None	No
Refresh Contacts	Purite	Yes
Refresh Endura	None	No
Refresh Liquigel	Purite	Yes
Refresh Optive Fusion	Purite	Yes
Refresh Optive Fusion Sensitive	None	Yes
Refresh Plus	None	Yes
Refresh Tears	Purite	Yes
TheraTears Contact Lens Comfort Drops	Patented preservative	Yes
TheraTears Dry Eye Therapy	Sodium perboate	Unknown
TheraTears Dry Eye Therapy Nighttime	None	Unknown
TheraTears Dry Eye Therapy Preservative Free	None	Unknown
Sodium carboxymethylcellulose /Polysorbate 80		
Refresh Optive Advanced	Purite	Yes
Refresh Optive Advanced Sensitive	None	Yes
Dextran 70 0 / Hypromellose		
Bion Tears - Systane	None	No
Tears Naturale II	Polyquad	Yes
Tears Naturale Forte	Polyquad	No
Tears Naturale Free	None	Yes
Hypromellose (hydroxypropyl methylcellulose)		
Genteal	Sodium perborate	No
Isopto Tears	BAK	No
Systane Gel	No	No
Visine for Dry Eye – Tired Eye Relief	BAK	No
Visine for Dry Eye – Environmental Relief	Disodium EDTA	Yes
Visine for Dry Eye – Eye Revival	Disodium EDTA	Yes
Blink-n-clean Lens Drops	Polyhexamethylene biguanide	Yes
Hydroxypropyl-guar (HP-guar)		
Systane Ultra	Polyquaternium-1	Yes
Systane Ultra Hydration	Polyquaternium-1	Yes
Mineral Oil		
Systane Balance	Polyquaternium-1	No
Mineral Oil / White Petrolatum		
Lacri-Lube	Chlorobutanol	No
Duolube	None	Unknown
Systane Ointment (also contains lanolin)	None	No
Polyvinyl alcohol		
Refresh	Sodium chlorite	No
Tears Plus	Chlorobutanol	Unknown
Murine Tears	BAK	No
Propylene Glycol / Polytheylene Glycol 400		
Dry Eyes Soothe (previously Moisture Eyes)	BAK	No
Systane	Polyquaternium-1	No
Systane Ultra High Performance	Polyquaternium-1	Yes

Product	Preservative	Contact Lens Compatible
Systane Ultra High Performance Preservative Free	None	Yes
Systane Balance	Polyquaternium-1	No
Blink Tears (also contains sodium hyaluronate)	Sodium chlorite	Unknown
Blink Tears Preservative Free	None	Unknown
Carbomer / Medium Chain Triglycerides		
Liposic drop/gel	Cetrimide	No
Systane Gel	Sodium perborate	No
Tear-Gel	Unknown	Unknown
Castor oil emulsions		
Refresh Ultra	Purite	Unknown
Refresh Endura	None	Unknown
Sodium hyaluronate		
Systane Ultra Hydration (also contains propylene glycol & polyethylene glycol)	Polyquad	Yes
Blink Contacts	Oxychloro complex	Yes
HYLO	None	Yes
HYLO DUAL	None	Yes
HYLO GEL	None	Yes
Vitamin A		
OCUNOX	None	N/A (HS administration)
Isotonic Solution		
Renu Lubricating Drops (Bausch & Lomb)	EDTA	Yes

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Useful tables from Canadian Glaucoma Guidelines 2009, 2017:

Recommendations for staging degree of glaucomatous damage and target IOP [2017]

Stage	Visual Field Changes	Optic Nerve and Retinal Nerve Fiber Layer (RNFL)	Suggested initial target pressure
Early/Mild	Mean Deviation (MD) < -5dB AND • < 18 points below 5% • < 10 points below 1% on pattern standard deviation (PSD) • No central points < 20 dB	• Thinning of superior and/or inferior rim (e.g. C/D < 0.65 in an average sized nerve) • No wedge defects	20-30% lowering Consider lowering an additional 10% if < 50 yrs, African North American descent or sibling with advanced glaucoma.
Moderate	• -5dB < MD < -10dB OR • 18-36 points below 5% OR • 10-20 below 1% on PSD OR • Central points between 10-20 dB in one hemifield	• Early notch in superior OR inferior OR relative thinning in both superior or inferior rim (e.g. C/D 0.7-0.85 in an average sized nerve) • Prominent wedge superior or inferior	30-40% lowering
Advance	• MD > -10dB OR • > 36 points below 5% OR • > 20 points below 1% on PSD OR • < 20 dB in both hemifields centrally OR • Any point in central 5 degrees < 10dB	• Early notch superior and inferior or complete notch (e.g. C/D > 0.9 in an average sized nerve) • Complete Wedge	40-50% lowering

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	

ALPHAGAN	37
Apraclonidine	37
AZARGA	37
AZOPT	37
BETAGAN	37
Betaxolol	37
BETOPTIC S	37
Bimatoprost	37
Brimonidine	37
Brinzolamide	37
COMBIGAN	37
COSOPT	37
Dipivefrin	37
Dorzolamide +/- Timolol	37
Drug-Induced Glaucoma	37

DUOTRAV	37
Echothiophate	37
Glaucoma	37
Intraocular Pressure	37
IOPIDINE	37
IZBA	37
Latanoprost	37
Latanoprostene	37
Levobunolol +/- Dipivefrin	37
LUMIGAN	37
Netarsudil	37
PHOSPHOLINE IODIDE	37
Pilocarpine	**37**
PILOPINE-HS	37
POAG	37
Primary Open Angle Glaucoma	37
PROBETA	37
PROPINE	37
ROCKLATAN	37
SAFLUTAN	37
SIMBRINZA	37
Tafluprost	37
Timolol/Latanoprost	**37**
Timolol/Pilocarpine	37
TIMOPTIC Reg & XE	37
TIMPILO 2 & 4	37
TRAVATAN	37
Travoprost	37
TRUSOPT	37
VISTITAN	37
VYZULTA	37
XALACOM	37
XALATAN	37
ZIOPTAN	37

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Health Canada July/19 is advising consumers that it has seized three unauthorized eye health products—**Digi Eye** contains neostigmine methylsulfate, **Kobayashi Aibon/Eyebon** Eyewash contains aminocaproic acid and **Sante FX Neo** contains neostigmine methylsulfate and aminocaproic acid—from a Glorious Cosmetics store in Edmonton, Alberta (10706, 82 Avenue NW) because they may pose serious health risks.

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Other drugs for Glaucoma:

- Osmotic Agents (used for acute rises in IOP)
  - Glycerol – onset 10 min; max effect in 1-2 hours
  - Mannitol – Onset 10-30min; max effect in 1 hour
- Cannabis, lower IOP by various modes of administration including inhalation, oral, intravenous, sublingual and topical
  - Topical
    - Poor ocular penetration due to high lipophilicity and low aqueous solubility of the cannabinoid extracts
    - Some studies have failed to find a hypotensive effect
    - Local irritation & corneal injury
  - Oral
    - Variable absorption, maximum hypotensive effect occurs between 60-90 min, duration of action between 3-4 hours
  - Smoked THC
    - Noted to lower intraocular pressure in 1971
    - AE: psychotropic effects (euphoria, dysphoria, decreased short-term memory, cognitive impairment, time distortion, decreased coordination, sleepiness), tachycardia, palpitations, systemic hypotension, conjunctival hyperemia, emphysema, possible lung cancer, addiction/tolerance, increased risk of motor vehicle accidents
  - Bottomline; Canadian Ophthalmological Society does not support medical use of cannabis for the treatment of glaucoma due to the short duration of action, the incidence of undesirable psychotropic and other systemic effects, and the absence of scientific evidenced showing a beneficial effect on the course of the disease. This is in contrast to other more effective and less harmful medical, laser, and surgical modalities for the treatment of glaucoma.

Clinical use of selected allergy products

	rhinorrhea (runny nose)	sneezing	nasal congestion	sinusitis (acute or chronic)	nasal polyps	allergic conjunctivitis	urticaria (hives)
Intranasal steroids e.g. **NASONEX**, **OMNARIS**, **FLONASE**, etc.	✓	✓	✓	✓	✓	**sometimes** helps with ocular symptoms of allergic rhinitis	
Oral antihistamines e.g. **REACTINE**, **CLARITIN**, **ALLEGRA**, etc.	✓	✓	desloratadine or cetirizine may help			✓	✓ (and OK to use very high dose fexofenadine in unresponsive chronic urticaria, e.g. 240mg BID)
Ophthalmic antihistamines e.g. **PATANOL**, etc.						✓ (equally effective vs oral antihistamines)	
Intranasal antihistamines e.g. **LIVOSTIN** (Canada) **ASTELIN** (USA)	✓	✓	✓	**DYMISTA** (fluticasone/azelastine) combines an intranasal steroid with an intranasal antihistamine.			
Oral decongestants e.g. **SUDAFED**, etc.			✓ **short term use only!**	occasional benefit in acute sinusitis - **short term use only!**			
Intranasal decongestants e.g. **OTRIVIN**, etc.							
Intranasal antimuscarinics e.g. **ATROVENT nasal spray**	✓						
Leukotriene receptor antagonists e.g. **SINGULAIR**	✓ (relieves symptoms of allergic rhinitis, but inferior to intranasal steroids)						
Intranasal cromolyn e.g. **RHINARIS-CS**	✓ (relieves symptoms of allergic rhinitis, but inferior to intranasal steroids)						
Ophthalmic mast-cell stabilizers e.g. **OPTICROM**, **ALOMIDE**, **ALOCRIL**, etc.						✓ (requires ~10 days before onset)	
Sinus steroid implant e.g. **SINUVA**					✓		
Saline irrigation e.g. **NETI-POT**				✓ (small benefit)			

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TYPE 2 DIABETES MELLITUS: PREVENTION & MANAGEMENT

Diabetes Canada (DC)'18, (previously CDA), ADA'19, ACP'18, C-Change'18

L Regier BSP, D Bunka BscPharm © www.RxFiles.ca Apr 2020

Background Information

- T2DM ranges from predominant insulin resistance to a predominant insulin secretory defect.
- ↑risk of *many* complications, including: CVD (e.g. MI), stroke, CKD, neuropathy, infection etc.
- **Drug induced hyperglycemia** (may cause poor glycemic control or induce T2DM): antipsychotic, clozapine, olanzapine steroids, cyclosporine, diuretic, e.g. >25mg hydrochlorothiazide estrogen, GnRH agonist, interferon alpha, nicotinic acid, ↑dose octreotide, pasireotide, phenytoin, sympathomimetic decongestant, siro-, tacro-, temsiro-limus, statin, tesamorelin, thyroid hormones; parenteral/enteral nutrition
- **Prevention**: in "prediabetes" (IFG, IGT or A1C 6.0-6.4% DC) lifestyle modification (see below) DPP, FDP may reduce progression to diabetes; also may consider metformin, DPP ?bariatric surgery role
- **Special populations**: Indigenous (↑ risk ∴ ↑ screening), pregnancy (peri-preg Pg 167), frail elderly (↑ risk hypoglycemia, consider time to benefit: statins ≥4yrs; intensive glycemic control >5-10yrs)

Pearls of Diabetes Care DC (see Diabetes Canada Sample Diabetes Patient Care Flow Sheet for Adults)

A	**A1C control**	Individualize! ≤7% for most; **minimize hypoglycemia** (see Pg 40 & 49)
B	**Blood Pressure control**	<130/80mmHg; some controversy with target (see below)
C	**Cholesterol control**	LDL <2mmol/L or >50% reduction, non-HDL <2.6 or apo B <0.8g/L
D	**Drugs to ↓CVD**	Indication for ACEI/ARB, statin, ASA, SGLT2 inhibitor or GLP1 RA
E	**Exercise & Health Eating**	**Both→** Aerobic: >150mins/wk & Resistance: 2-3 times/wk
S	**Screening**	See below
S	**Smoking Cessation**	If smoker, ask for permission, then provide support (see Pg 196)
S	**Self-Management**	Adherence, sick day management (SADMANS), daily foot/leg exam www.diabetes.ca/diabetes-and-you/healthy-living-resources

Risk Factor Modification

(requires ongoing assessment, shared decision making, & ideally an inter-professional diabetes care team); CV risk calculators for T2DM: ADVANCE risk score & DIAL model; www.u-prevent.com

Nutrition

(may ↓ A1C by 1-2%) {note: % of energy or total calorie/day is a guide; individualize}

- Consider patient's cultural & nutritional preferences. Enlist dietician support. Maintain regular timing & meal spacing to optimize BG. Consider Mediterranean or DASH diet features. ↓ sweetened drinks.
- *CHO: ~45-60% of energy or total calories/d*; ensure consistent CHO intake at meals; replace high-glycemic index with low-glycemic index CHO (e.g. whole grains, fruit, vegetables, legumes) ↓PPG
- *Protein: ~15-20% of energy or total calories/day*; may consider lean or vegetable protein
- *Fat: ~20-35% energy or total calories/d*; ↓ trans & saturated fats; ↑ omega-3 & plant oils, nuts
- Diabetes plate method: small plate - ½ non starchy vegetables, ¼ starchy CHO, ¼ lean protein
- Low caloric diet (~850 calories/d x 3-5 mos) ↑ remission DiRECT but real world pt applicability unclear

A1C

target: individualize! ≤7% for most, but for some ≤6.5 or ≤8-9 (frail elderly); (re-evaluate over time as disease progresses & patients age) (see Pg 40)

- **Screening**: every 6 months to 3 years depending on risk (see Pg 40)
- SMBG: consider benefits, harms, & costs; useful if helps with behaviour change (see Pg 43)
- Metformin is the first line agent. DC (may also be used for prevention in those with prediabetes DPP)
- Antihyperglycemic with CVD benefit: (consider adding to metformin if established CVD, see Pg 40-42)
  - Empagliflozin ☎ ▼ DC(1,1A), ADA(A) or liraglutide ✗ ⊗ DC(1,1A), ADA(A) or canagliflozin ☎ ✆ DC(C2), ADA(C)
  - Empagliflozin ☎: fail trial of metformin alone & defined CVD; empagliflozin ☎▼ & canagliflozin ☎✆: fail trial of metformin & sulfonylurea, & not used with DPP4 inhibitor; liraglutide ✗⊗; semaglutide ✗▼

Physical Activity

(↓A1C ~0.7% & morbidity/mortality) See RxFiles: Physical Activity Rx

- Aerobic: >150 min/week (over 3+ days/week) of ≥ moderate activity ADA(B) (e.g. brisk walking after meals ↓PPG, consider pedometer) but may start gradually with 5-10mins *in addition to resistance training*
- Resistance: 2-3 times/week of e.g. 1 set of 5 exercises ADA(B) *in addition to aerobic activity*
- Flexibility or balance training (e.g. tai chi or yoga) may be helpful & get up from sitting q 20-30mins!

Blood Pressure

target: SBP <130 DC(C,3)/DBP <80 DC(A,1A), C-CHANGE (caution: autonomic neuropathy, frail elderly)

- **Screening**: once yearly, if elevated then every 3-6 months (3 BP readings recommended at each visit)
- *Controversy* regarding target; others target <140/90 ADA(A) if ASCVD <15% & <130/80 ADA(C) if ASCVD>15%
- If CVD or CKD: ACEI/ARB 1st-line; otherwise may use either ACE, ARB, long acting DHP-CCB or diuretic. If combo tx required ACEi + DHP-CCB preferred over ACEI + diuretic ACCOMPLISH

Weight Loss

(optimal: ↓ 1-2kg/month; ~500kcal/day energy deficit)

- Goals: ↓ Wt (≥5% ADA of initial weight), then maintenance of and sustaining weight loss
  - ↓ 5% to 10% initial body weight in overweight T2DM can result in improved BG, lipid & BP control
- RCT (exercise 175min/week + diet) targeted 7% ↓ weight/10y → reduced meds & A1C LOOK AHEAD
- 12 mos intensive weight loss management (↓ ~10kg)→ cessation of meds and ↑ remission DiRECT
- If failure to obtain glycemic control & ↑ weight may consider: GLP1 agonist (e.g. liraglutide ✗⊗ DC(A,1A), semaglutide ✗⊗) or orlistat ✗⊗ DC(A,1A) if BMI ≥27 ADA(A) or bariatric surgery if BMI ≥30 ADA or ≥35 DC(A,1A)

Cholesterol

target: LDL<2 <1.8 if CVD or 10yr ASCVD>20% ADA or >50% ↓, non-HDL <2.6mmol/L or apo B <0.8g/L

- **Screening**: lipid profile once/yr, if ↑ then every 3-6 mons (4-12 wks after statin initiation/change dose)
- Statin recommended: CCS established CVD, ≥40yrs 40-75yrs & LDL ≥1.8 AHA'18, <40yrs & diabetes for >15yrs & age >30yrs, or microvascular complication eg CKD (see Pg 50 for T2DM primary prevention trials HPS, CARDS)
- If not at target or statin intolerance & established CVD, may consider ezetimibe, or PCSK-9 inhibitors (but no long-term safety and ↑↑cost); fibrates or niacin are not generally recommended ADA(A)
- If fasting serum TG >10mmo/L, may use fibrate to reduce pancreatitis risk (↑myopathy with gemfibrozil + statin)

- **Limit Alcohol**: ♀ ≤2 drinks/day & <10 drinks/week; ♂ ≤3 drinks/day & <15 drinks/week. Caution: Alcohol may cause delayed hypoglycemia and has the potential to cause weight gain (extra calories)
- **Smoking Cessation**: including e-cigarettes ADA(A); e-cigarettes and vaping use is associated with lung injury and is not a safer alternative to cigarettes CDC '20 See Smoking Cessation Chart Pg 196
- **Immunizations**: Influenza annually, Pneumococcal vaccine, Hepatitis B?
- **Herbals**: insufficient evidence to recommend cinnamon, vitamins D, E, C ADA(C)

Renal Protection

normal: ACR <2mg/mmol; eGFR >60mL/min

- **Screening**: eGFR & ACR yearly, if abnormal then every 3-6 months
- BP & BG control are important to prevent/delay renal disease (↓ albuminuria, lack hard renal outcome data)
- ACEI/ARB recommended if: established CVD, DC(A,1) age ≥55 years with additional risk factors or end organ damage (ACR≥ 2, retinopathy, LVH) DC(A,1) or microvascular complications DC(D,consensus)
- CKD & ≥50yrs (no dialysis): initiate statin ± ezetimibe CCS'16(SR,HQE), SHARP • Consider SGLT2 inhibitor ADA(A)

Should I recommend aspirin?

Aspirin 81mg po daily is **recommended in *all* patients with CVD** (e.g. CAD, stroke, PAD) consistently among guideline groups. *Controversy regarding use in* primary prevention due to inconsistent benefits among studies & systematic reviews and documented harm (↑GI bleed). ASCEND

Routine use is *not* recommended; DC(A,1A) may consider if multiple CV risk factors DC(D), ADA(C) See RxFiles "ASA for Primary Prevention of Cardiovascular Disease"

Management of Other Diabetic Complications

• See Erectile Dysfunction Chart Pg 73

- **Diabetic Neuropathy**: tricyclic antidepressants (TCAs), duloxetine, gabapentinoids (see Pg 122)
- **Gastroparesis**: ↓ glucose; caution with GLP1 agonists (also, DPP4 inhibitors, metformin); if severe, use prokinetic eg domperidone, metoclopramide as needed
- **Nonalcoholic Fatty Liver Disease**: ↑LFTs, fatty liver on ultrasound → refer; Tx: Wt loss, ↓ glucose

Other Screening

- **Retinopathy**: every 1-2yrs or ≤ 1yr if retinopathy present
- **Cardiac**: resting ECG every 3-5 years if >40 years or diabetes complications present
- **Foot**: 10g monofilatment / 128 Hz tuning fork, skin changes, pulses yearly; ↑ if abnormalities
- **Depression** (PHQ-9), **Anxiety** (GAD), Cognitive Impairment, Frailty

☎=Exception Drug Status in SK ✗=Non-formulary in SK ⊗=not covered by NHB **A1C**=glycosolated Hemoglobin **ACR**=albumin to creatinine ratio **ACS**=acute coronary syndrome **BG**=blood glucose **BMI**=body mass index **CHO**=carbohydrate **CKD**=chronic kidney disease **CVD**=cardiovascular disease **DBP** = diastolic blood pressure **DKD**= diabetic kidney disease **GI**=gastrointestinal **HDL**=high density lipoprotein **IFG**=impaired fasting glucose **IGT**=impaired glucose tolerance **LDL**=low density lipoprotein **MI**=myocardial infarction **PPG**=postprandial blood glucose **SMBG**=self monitoring blood glucose **T2DM**=type 2 diabetes mellitus **tx**=treatment **Wt**=weight

Online Extras:

T2DM Multifactorial Approach:

STENO-2: n=160, T2DM & microalbuminuria; multifactorial intensive (A1C <6.5% <20% achieved @13yrs, 8.4→7.7%; BP, lipid, ACEI, ASA) vs conventional tx for 7.8yr+ 5.5yr f/u; ⇨ ↓death, NNT=5 / 13.3yr p=0.02, ↓ macro & microvascular events. (Only 1 pt achieved all 5 targets at 13yrs). 21yr f/u ⇨ 7.9yrs gained

ADDITION-Europe: n=3057 new T2DM, age ave ~60; **5.3yrs**; multifactorial intensive (A1C, BP, ACEI, TC, lifestyle) ⇨ slightly improved surrogates (A1C, LDL, BP) but **non-significant** ↓ in CV events/death (7.2% vs 8.5%; HR 0.83, 95% CI: 0.65-1.05) & microvasc complications. 10yr follow-up: CV events and mortality remained **NS.** 2019

Metabolic Syndrome: condition characterized by a distinctive cluster of abnormalities including: abdominal obesity, HTN, dyslipidemia, insulin resistance & dysglycemia.

In-Hospital Considerations (insulin considered a "high-risk" medication due to administration errors & risk of harm)

- Scheduled basal, bolus & correction (supplemental) insulin is preferred over "sliding-scale" insulin as ↓hyperglycemia DC(A,1A)
- Targets: noncritically ill (e.g. medicine ward) FBG: 5-8, random BG <10; critically ill (e.g. ICU) FBG 6-10 mmol/L DC(D) (targeting ↓ levels controversial eg 4.4-6.1 CV surgery) NICE-SUGAR

CAD Risk in Diabetes

- Diabetes confers ↑ CAD risk such that those with diabetes, ♂ age ≥45 or ♀ age ≥50yr, are considered to be at high CAD risk. For specific estimates, see a risk calculator (e.g. UKPDS).[i]

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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DIABETES: Modifiable Risk Factors for Cardiovascular & Renal Protection

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Acute kidney injury = ↑SCr by 26.5 micromol/L over 48 hrs, **OR** ↑SCr by 1.5x baseline in last 7 days, **OR** urine volume <0.5 mL/kg/hour over six hours.[26]

Online Extras: Diabetes and the Kidneys

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Table 1: Definition of Chronic Kidney Disease[26]

CKD	eGFR <60ml/min	and/or	Albuminuria	and/or	Markers of Kidney Damage

Chronic kidney disease is defined as structural or functional abnormalities of the kidneys for ≥ **3 months**.

There are 3 ways to identify damage: an eGFR calculation; albuminuria; or through markers of kidney damage.

GFR: a marker of renal excretory function

Stage	Description	GFR (mL/min/1.73m^2)
1	Kidney Damage with normal or increased GFR	>90
2	Mild ↓ eGFR	60-89
3a	Mild to moderate ↓eGFR	45-59
3b	Moderate to severe ↓eGFR	30-44
4	Severe ↓ eGFR	15-29
5	Kidney Failure	<15 (or dialysis)

Albuminuria: marker of glomerular injury

Albumin to creatinine ratio (ACR): detects elevated protein in a spot urine test and is more convenient than 24-hour collection gold standard

Dipstick test: detects abnormalities in the urine.

Stage	Urine ACR* (mg/mmol)	Dipstick
Normal	<2	– to trace
Microalbuminuria	2-20	Trace to +
Macroalbuminuria	>20	+ or greater

* Diabetes Canada

- Urine sediment abnormalities
- Electrolyte or other abnormalities due to tubular disorder
- Abnormal histology
- Abnormal structure detected through imaging
- History of kidney transplant

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Notes / References for Diabetes Agents Colour Outcomes Comparison Chart (www.RxFiles.ca)

Death/MACE (MACE: Major adverse cardiovascular event)

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 Acarbose vs placebo; coronary heart disease (Chinese) HR 0.98 95% CI, 0.86-1.11, p=0.73.[13] ACE
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]
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%

Death/MACE (MACE: Major adverse cardiovascular event)- cont'd

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

Insulin degludec vs insulin glargine (T2DM; ~50/50 split bolus vs bolus/basal baseline & no difference between basal/bolus insulin use between groups at the end of study): MACE 8.5% vs 9.3% (95% CI 0.78- 1.06; p<0.001 non-inferiority).[34a] DEVOTE

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/5 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. DPP4-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

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 vs placebo; MACE 12.4% vs 12.1% **non-inferior** (p<0.001), but not superior (p=0.74).[18] CARMELINA Linagliptin vs glimepiride: MACE 11.8% vs 12% non-inferior (p<0.001) but not superior.CAROLINA2019
12. Liraglutide vs placebo; **MACE** 13% vs 14.9%, **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 SC weekly vs placebo; MACE **superior**; (nephropathy was better; however, retinopathy complications were worse).[20] SUSTAIN6
13. Lixisenatide vs placebo (post-ACS); MACE 13.4% vs 13.2%, **non-inferior** (p<0.001), not superior (p=0.81).[21] ELIXA
14. Exenatide extended release vs placebo (~70% CVD, ~30% primary prevention); MACE 11.4% vs 12.2% over median 3.2 yr, **non-inferior** (p<0.001), but not superior (p=0.06).[22] EXSCEL Dulaglutide[USA] CV trial ongoing, estimated completed 2018.[23] REWIND Albiglutide CV trial ongoing, estimated completed 2018.[24] HARMONY Semaglutide PO CV trial semaglutide po vs placebo: MACE, non-inferior; ↓ all-cause death 1.4% vs 2.8% 2ndy endpoint 2019. PIONEER-6
15. Empagliflozin vs placebo; **MACE** 10.5% vs 12.1%, **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 Canagliflozin vs placebo; **MACE** 26.9/1000ptyrs (2.7%/yr) vs 31.5/1000ptyrs (3.15%/yr), **superior** (p=0.02, **NNT~220/yr**), f/u duration 3.6yr, no signfigant difference in components of primary composite or death; ↑ 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. [26,27,27a] CANVAS Dapagliflozin vs placebo; MACE 8.8% vs 9.4% p<0.001 **non-inferior**, but not superior p=0.17; ↓ CV death & HF hospitalization combo outcome.[28] DECLARE
16. Sotagliflozin CV trial ongoing, estimated completed 2022. SCORE
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]

HF/Edema- cont'd

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] Linagliptin vs placebo; hospitalization for heart failure 6.0% vs 6.5% for an absolute incidence rate difference of −0.27 (95% CI, −0.82 to 0.28), with no significant difference between the 2 treatment groups (HR, 0.90; 95% CI, 0.74-1.08; P = .26).CARMELINA
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 Empagliflozin in HF patients (regardless of diabetes status) ongoing trial estimated to be complete 2020 EMPEROR-Reduced & Preserved. Canagliflozin vs placebo; hospitalization for HF: 5.5/1000ptyrs (0.55%/yr) vs 8.7/1000ptyrs (0.87%/yr) (HR 0.67, 95% CI 0.52-0.87) follow up 3.6yr but exploratory.[27a] CANVAS Dapagliflozin vs placebo; hospitalization for HF: 2.5%/1000 patient year vs 3.3%/1000 patient year HR0.73 (95% CI 0.61-0.88) but exploratory.[28] DECLARE Dapagliflozin 10mg po once daily vs placebo; composite primary outcome: worsening HF (hospitalization or urgent visit resulting in IV therapy for heart failure) or CV death:
16.3% vs 21.2% p=<0.001. DAPA-HF
33. Basal insulin (glargine) vs standard care; hospitalization for HF 4.9% vs 5.5% p=NS.[21] ORIGIN
34. Basal insulin vs basal/bolus insulin; small sample n=152; HF 1.3% vs 5.3% p=NS.[22] ArchInternMed1997

- sitagliptin ↑ ≤ 0.5 kg/12 weeks[10]

A8. GLP1 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 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 NNH=250/3 yr**.[7] DREAM
28. Acarbose vs placebo; impaired glucose tolerance; HF 0% vs 0.3% p=N/A.[8] STOP-NIDDM

Other- continued

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 (DPP-4 inhibitors and GLP1 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. SGLT2 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]

Other/Additional Trials Recently Published

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 (DPP-4 inhibitors and GLP1 agonists) ?↑ pancreatitis:[24] Meta-analysis of SAVOR-TIMI 53, EXAMINE, & TECOS (n=36,395) demonstrated ↑ acute pancreatitis **OR 1.79 (1.13-2.82) and ARI of 0.13%** vs placebo.[24a] US case control study; incretin agent (exenatide or sitagliptin) within 30 days **OR 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
    - ?↑ fracture; canagliflozin 100 mg-300 mg vs placebo follow up 3.6yr; 15.4/1000ptyrs (1.54%/yr) vs 11.9/1000ptyrs (1.19%/yr) NNT= 285/yr (HR 1.26, 95% CI 1.04-1.52),. CANVAS ?↓BMD (total hips, lumbar spine, femoral neck, & distal forearm).[41]
    - ?↑ lower limb amputation; canagliflozin 100-300 mg vs placebo follow up 3.6yr; ↑ all amputation 6.3/1000ptyrs (.63%/yr) vs 3.4/1000ptyrs (0.34%/yr) NNH=345/yr (HR 1.97, 95% CI 1.41-2.75) & ↑ major amputation (ankle, below/above knee) 1.8/1000ptyrs (0.18%/yr) vs 0.9/1000ptyrs (0.09%/yr) NNH>1000/yr (HR 2, 95% CI 1.08-3.82) .CANVAS Other trials neutral.e.g.,CANVAS-R [42,43] May2017 FDA: canaglifozin -increased risk of leg and foot amputations. https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery
      Aug 2020 FDA: Removed lower limb amputation warning for canagliflozin.
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%); however recent real world surveillance data suggests this may not be an issue [47, 48] https://annals.org/aim/article-abstract/2739786/sodium-glucose-cotransporter-2-inhibitors-risk-severe-urinary-tract-infections?searchresult=1 .
    ↑ genital tract skin 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).
46. Canagliflozin 100mg once daily vs placebo: ↓primary composite outcome of ESKD, doubling of SCr & renal or CV death: 11.1% vs 15.5% p= 0.00001. CREDENCE
47. FDA Warning (May 2019): SGLT2 inhibitors associated with **Fournier Gangrene**. 55 cases reported to FDA between 2013-19 with SGLT2i. Likely class effect (cana = 21, dapa = 16, empa=18). 2019 review: https://annals.org/aim/article-abstract/2732837/fournier-gangrene-associated-sodium-glucose-cotransporter-2-inhibitors-review-spontaneous

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ANTI-HYPERGLYCEMIC TYPE 2 DIABETES AGENTS: Drug Comparison Chart, Online Extras

Complete ABBREVIATIONS: =↓ dose for renal dysfunction =↓ dose for hepatic dysfunction ς=scored tab $=total cost in SK ☎=Exception Drug Status (EDS) in SK ✗=Non-formulary in SK ✆=prior approval for non-insured health benefits for First Nations (NIHB) ⊗=not covered by NIHB ▼=Covered by NIHB & ONLY for those drugs which have SK Formulary restrictions such as EDS or non-formulary status ✓=Health Canada Indication ❄=refrigerate ♀=female **1º**=primary **A1c**=glycosylated hemoglobin **ac**=before meals **ACP**=American College of Physicians **ADA**=American Diabetes Association **AE / AE(s)**=adverse effect(s) **AFP**=American Family Physcians **AKI**=acute kidney injury **am**=morning **AST**=asparate aminotransferase **BB**=beta blocker **BID**=twice daily **BG**=blood glucose **BP**=blood pressure **CA**=cancer **cc**=with food **CDN**=Canadian **CHO**=carbohydrate **CI**=contraindicated **CKD**=chronic kidney disease **CV**=cardiovascular **CVD**=cardiovascular disease **D**=diarrhea **D/C**=discontinued **DC**=Diabetes Canada **DI**=drug interaction **DKA**=diabetic ketoacidosis **DM**=diabetes mellitus **DPP4**=dipeptidyl peptidase-4 **dx**=disease/diagnosis **eGFR**=estimated glomerular filtration rate **ER**=extended release **EtOH**=alcohol **EU**=Europe **FDA**=US Food and Drug Administration **Fe^{++}**=iron **g**= generic **GERD**=gastroesophageal reflux disease **GI**=gastrointestinal **GLP1**=glucagon-like peptide-1 **HA**=headache **HD**= hemodialysis **HF**=heart failure **hr**(s)=hour(s) **HS**=bedtime **hx**=history **IBD**=inflammatory bowel disease **IBS**=irritable bowel syndrome **IFG**=impaired fasting glucose **IGT**=impaired glucose tolerance **kg**=kilogram **LFT**=liver function test **MACE**=major adverse cardiovascular events **MAOI**=monoamine oxidase inhibitor **MI**=myocardial infarction **N**=nausea **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-significant **po**=oral **PPG**=postprandial blood glucose **PCOS**= polycystic ovary syndrome **PD-CKD**=peritoneal dialysis for chronic kidney disease **pm**=evening **po**=by mouth **REMS**=risk evaluation and mitigation strategy **subcut**=subcutaneous **SGLT2i**=sodium-glucose cotransporter-2 inhibitor **SU**=sulfonylurea **SGLT2**=sodium-glucose cotransporter-2 **SIADH**=syndrome of inappropriate antidiuretic hormone secretion **SJS**=Stevens-Johnson Syndrome **SK**=Saskatchewan **T1DM**=type 1 diabetes mellitus **T2DM**=type 2 diabetes mellitus **TID**=three times daily **TZD**=thiazolidinediones **URTI**=upper respiratory tract infection **US**=United States **UTI**=urinary tract infection **V**=vomiting **wk(s)**=week(s) **Wt**=weight **XR**=extended-release **yr(s)**=year(s)

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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**.
FDA May/17: Based on new data from two large clinical trials, the FDA has concluded that the type 2 diabetes medicine **canagliflozin** (Invokana, Invokamet, Invokamet XR) causes an **increased risk of leg and foot amputations**. FDA is requiring new warnings, including the most prominent Boxed Warning, to be added to the canagliflozin drug labels to describe this risk.
FDA Aug/18: is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene.
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Health Canada Dec/05 Association of **AVANDIA** & **AVANDAMET** with new onset and/or worsening of **macular edema** http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/avandia_avandamet_hpc-cps_e.html
Health Canada Jan/06 & July/07 Association of **AVANDIA** & 6 reports of parotid gland enlargement http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n1_e.html#2
Health Canada Apr/07 is warning consumers from The Hong Kong Department of Health found **Lanmei Keili Ji to be adulterated with gliclazide**, a hypoglycaemic agent (lowers blood sugar).
Health Canada May/07 is advising consumers not to use **Xiaokeshuping Jiangtangning Jiaonang** capsules in Hong Kong to contain the undeclared pharmaceutical drugs phenformin, rosiglitazone, and glibenclamide, which may be used in diabetes to lower blood sugar.
Health Canada May& June/07 is advising consumers & health professionals about heart risks with **Avandia** http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/2007/avandia_pc-cp_3_e.html
Health Canada Sept/07 is advising consumers not to use foreign health products due to concerns about possible side-effects: **Jacaranda**, **Queenmer Fat Loss**, **Li Da Dai Dai Hua Jiao Nang, J-minus** and **Jelimel Slimming Capsules**. These products are promoted for weight loss and have been found to be adulterated with the prescription drug sibutramine. Sibutramine is used for treating obesity and should only be taken under the supervision of a health professional. **Junyu Jiaonanyihao** has been found to contain the undeclared prescription drugs sibutramine and dexamethasone, as well as phenolphthalein, which is currently prohibited in Canada.. **Heng Tong Jiangtangning Jiaonang** was found to contain the prohibited drug phenformin, and the prescription drug glibenclamide (glyburide) which should only be taken under the supervision of a health professional.
Health Canada Nov/07 Rosiglitazone (**AVANDIA**®) is no longer approved as monotherapy for type 2 diabetes, except when metformin use is contraindicated or not tolerated. Rosiglitazone is no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated. Treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure (i.e., NYHA Class I, II, III or IV).
Health Canada April/08 warns that Singapore's Health Sciences Authority (HSA) advised the public not to use the product **Power 1 Walnut**, because it was found to contain the prescription drugs sildenafil and glibenclamide.
Health Canada April/08 is advising consumers not to use The Hong Kong Department of Health advised the public not to use the product **Tian Sheng Yi Bao** because it was found to contain two pharmaceutical products, glibenclamide and phenformin.
Health Canada June/08 **Nangen Zengzhangsu** (may also be known as Nangen or Nangeng), Sanbianwan, Jiu Bian Wang, Tian Huang Gu Shen Dan, Zui Xian Dan Gong Shi Zi, and Power Up. The Hong Kong Department of Health has warned consumers not to use these herbal/proprietary Chinese medicine products promoted for erectile dysfunction because they have been found to contain sildenafil and/or glibenclamide.
Health Canada June/08 **Zhong Hua Niu Bian**. Zhong Hua Niu Bian is an herbal/proprietary Chinese medicine product promoted for erectile dysfunction. Singapore's Health Sciences Authority has warned against the use of this product because it has been found to contain sildenafil, glibenclamide, tadalafil and sibutramine
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**.
Health Canada Jul/17 is advising Canadians that Novo Nordisk A/S has updated a voluntary recall of insulin cartridge holders used in certain lots of its **NovoPen Echo and NovoPen 5 insulin pens**. The company detected that the **cartridge holders may crack** or break if exposed to certain chemicals, such as some cleaning agents.
HEALTHY Study Group, A **School-Based Intervention** for Diabetes Risk Reduction. N Engl J Med 2010 0: NEJMoa1001933.
Health Canada Aug/15: Co-administration of **repaglinide and clopidogrel** (a CYP2C8 inhibitor) may lead to a significant decrease in blood glucose levels due to a drug-drug interaction. The concomitant use of repaglinide and clopidogrel is now contraindicated.
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.
Health Canada Aug/16: Hong Kong Department of Health-**TANGKE TEGONGYIHAOJIAONANG** undeclared phenformin and glibenclamide.
Health Canada Sep/17: **INVOKANA** (**canagliflozin**) and **INVOKAMET** (**canagliflozin** and metformin) - Risk of Lower Limb **Amputation** - Janssen Inc.
Health Canada Jan/18 - Summary safety review – dipeptidylpeptidase-4 inhibitors – assessing the potential risk of a skin reaction (bullous pemphigoid). January 25, 2018.
Health Canada Jun/18: Jamp-Glucose 50 and Jamp-Glucose 75 – **Risk of False Negative Oral Glucose Challenge** or Tolerance Test Results. Jamp Pharma Corporation has voluntarily recalled three (3) lots of Jamp-Glucose 50 and three (3) lots of Jamp-Glucose 75 because they contain significantly less D-glucose than what is declard on the label.
Health Canada Dec/19: is aware that some metformin products available outside Canada have been found to **contain a nitrosamine impurity**, N-nitrosodimethylamine (NDMA), above the acceptable limit.
Health Canada Feb/2020: Apotex Inc. is recalling eight lots of its 500 mg extended release metformin tablets (**"APO-Metformin ER"**) because they contain a nitrosamine impurity called N-nitrosodimethylamine (NDMA) above the acceptable limit.
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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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Insulin Pen Devices, Online Extras

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Abbreviations: **Rx**=prescription **yr(s)**=year(s)

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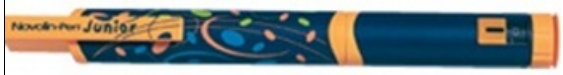
Discontinued Insulin Devices

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) {Green, Yellow} 1-35 units in ½ unit increments	 [Novo-Pen Junior was replaced by **NovoPen Echo**'2013]	**NovoLIN ge** (Toronto, NPH, 30/70, 40/60, 50/50) **Levemir** (detemir) **NovoRapid, Fiasp** (aspart) **NovoMix 30** (aspart + aspart protamine) **Tresiba** (degludec)	◆ 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) {Champagne, Burgundy} 1-60 units in 1 unit increments	 [HumanPen Luxura was replaced by **HumaPen Savvio**]	**HumuLIN** (R, N, 30/70) **HumaLOG** (lispro) **HumaLOG** Mix25 (lispro+lispro protamine) **HumaLOG** Mix50 (lispro+lispro protamine)	◆ 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
Humalog Pen **Humalog Mix Pen** 1-60 units in 1 unit increments	 [Humulog Pens were replaced by **Humalog KwikPen**'2011]	**HumaLOG** (lispro) **HumaLOG Mix 25** & **Mix 50** (lispro + lispro protamine)	◆ window magnification **NOT** as clear as other pens ◆ may use a symbol instead of 0 to indicate dose complete ◆ has dial back capability, decreases wastage ◆ audible click on dialing doses ◆ dark numbers on a white background
Humulin N Pen 1-60 units in 1 unit increments	 [Humulin N Pen was replaced by **Humulin N KwikPen**'2011]	**HumuLIN N** [Humulog and Humulin N Pens were replaced by Humalog and Humulin N KwikPen'2011]	

General Comments: Pen vs Vial/Syringe:

-Advantages: convenient; potentially less painful (need is not dulled entering vial stopper; discreet)

-Disadvantages: potentially more wastage of insulin, may require more injections (as insulins not mixed), little higher cost, upper limit to single dose

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Jet injectors (eg. AdvantaJet, Medi-Jector) avoid the use of needles, are expensive, & require frequent cleaning.

Insulin: Drug Comparison Chart, Online Extras

Complete ABBREVIATIONS: ↓ =↓ dose for renal dysfx $=total cost in SK (1500units = 50 units x 30 days) ☎=Exception Drug Status in SK ✗ =Non-formulary in SK ✆=prior approval for NIHB ⊗=not covered by NIHB ✓=Health Canada Indication ❄= refrigerate **A1c**=glycosylated hemoglobin **ABX**=antibiotic **AE(s)**=adverse effect(s) **BID**=twice daily **BG**=blood glucose **DKA**=diabetic ketoacidosis **DPP4**=dipeptidyl peptidase-4 **dysfx**=dysfunction **eGFR**=estimated glomerular filtration rate **FBG**=fasting blood glucose **FQ**=fluoroquinolone **GLP1**=glucagon-like peptide-1 **hr(s)**=hour(s) **HCV**=hepatitis C virus **HS**=bedtime **IM**=intramuscular **IV**=intravenous **kg**=kilogram **mo(s)**=month(s) **NPH**=neutral protamine Hagedorn **PK**=pharmacokinetics **RCT**=randomized controlled trial **subcut**=subcutaneous **SGLT2**=sodium-glucose cotransporter-2 **SMBG**=self monitor blood glucose **SSRI**=selective serotonin reuptake inhibitor **SU**=sulfonylurea **T1DM**=type 1 diabetes mellitus **T2DM**=type 2 diabetes mellitus **TID**=three times daily **TZD**=thiazolidinediones **Wt**=weight **yr(s)**=year(s)

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Originally Prepared by: M Jin PharmD, CDE (Hamilton); L. Regier BSP, BA; B. Jensen BSP; S Downey BSP

AFREZZA inhaled insulin: not in Canada rapid-acting insulin for adults with T1 and T2DM; no A1C difference from regular/NPH regimens but patients may prefer this route of administration; $$$

- **CI**: COPD, asthma, smoking if within prev 6 months, ketoacidosis; long-term safety ?cancer
- **AE**: cough, hypoglycemia, throat pain, **bronchospasm**, ?↓pulmonary fx tests short term, ?anti-insulin antibodies
- **Administration**: 8, 12 units (dry powder) given 20min ac

Mixing Insulins: NPH with insulin regular except ENTUZITY or rapid-acting analogues except HUMALOG 200units/mL, FIASP;
insulin vial & syringe preferred (although some use cartridge & syringe); **CI**: all long-acting analogues

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Insulin Initiation, Titration, & Follow up in T2DM, Online Extras

Complete ABBREVIATIONS

A1c=glycosylated hemoglobin **AE**=adverse events **am**=morning **BID**=twice daily **BG**=blood glucose **CGM**=continuous glucose monitoring **DPP4**=dipeptidyl peptidase-4 **eGFR**=estimated glomerular filtration rate **FBG**=fasting blood glucose **GLP1**=glucagon-like peptide-1 **HA**=headache **hr(s)**=hour(s) **HS**=bedtime **NPH**=neutral protamine Hagedorn **NPO**=nothing by mouth **po**=oral **PPBG**=postprandial (2hr) blood glucose **PRN**=as needed **subcut**=subcutaneous **SGLT2**=sodium-glucose cotransporter-2 **T2DM**=type 2 diabetes mellitus **tx**=treatment **yr(s)**=year(s)

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Additional Information:

Table 1. Potential Patient Barriers to Insulin Initiation and Strategies/Tools continued

- ADA Sample questions

Table 7—Sample questions to guide a person-centered assessment (56)

- How is diabetes affecting your daily life and that of your family?
- What questions do you have?
- What are one to two positive things you are doing right now to manage your diabetes?
- What is the hardest part about your diabetes right now, causing you the most concern, or is most worrisome to you about your diabetes?
- How can we best help you?

Table 2. Switching Insulins continued

Previous Insulin	New Insulin	Dosing Comments
rapid-acting insulin analogue APIDRA, HUMALOG, ADMELOG, NOVORAPID, FIASP	insulin regular HUMULIN R, NOVOLIN ge Toronto	switch on a unit-to-unit basis

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A1c	51
BASAGLAR	51
Detemir	51
Diabetes	51
Glargine	51
Glucose	51
HUMULIN L, N, Reg, U	51
Hypoglycemia	51
Insulin	51
LANTUS	51
LEVEMIR	51
NOVOLIN	51
TOUJEO	51
TRESIBA	51
Type 1 Diabetes Mellitus	**51**
A1c	52
ADMELOG	52
APIDRA	52
Aspart	52
BASAGLAR	52
Corticosteroid	52
Degludec	52

Detemir	52
Diabetes	52
Driving	52
ENTUZITY	52
FIASP	52
Glargine	52
Glucose	52
Glulisine	52
HUMALOG	52
HUMULIN L, N, Reg, U	52
Hypoglycemia	52
Insulin	52
LANTUS	52
Lispro	52
NOVOLIN	52
NOVOMIX	52
NOVORAPID	52
Time Zone	52
TOUJEO	52
Travel	52
TRESIBA	52
Type 1 Diabetes Mellitus	**52**
TRURAPI	52
Type 2 Diabetes Mellitus	51
Type 2 Diabetes Mellitus	52

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ONLINE EXTRAS: SELF-MONITORING OF BLOOD GLUCOSE IN TYPE 2 DIABETES

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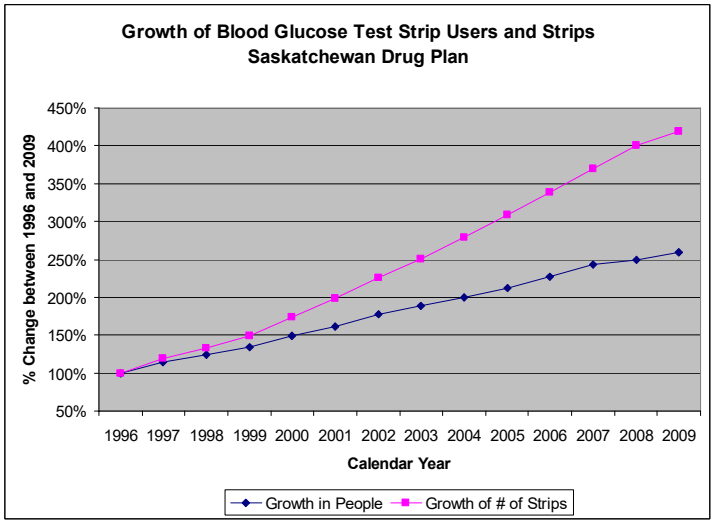
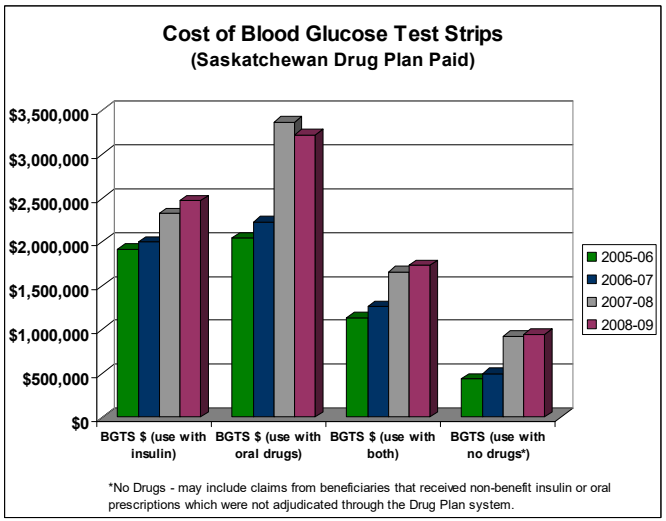
Background considerations:

- Weighing the benefits & risks of intensive therapy: [See also Diabetes - Landmark Outcome Trials Chart[i]]
  - 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.[ii] {The 10 year observational follow-up to the UKPDS suggests CV benefit of intensive glycemic control (FBG <6; mean baseline A1c 7.9% vs 8.5%) especially with metformin.[iii]}
  - Individualization of antihyperglycemic therapy has become a common theme[iv,v] 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%)[vi].
  - 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[vii] 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.[viii]

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.
[These results were prepared using data from Brogan Inc., a unit of IMS, PharmaStat®, Public and Private Drug Plans Databases, 2000-2011]

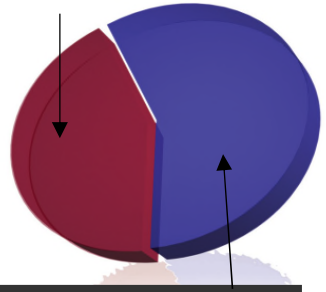
- Cost to drug plans public+private = $330 million 2006 Canadian data
- Cost per QALY (quality adjusted life year) is estimated at $113,643 for routine use of SMBG (at least 1 strip each day on average).
- Annual cost per patient: $165 - $2,400 (see Table below).





Patients with diabetes who are using insulin

$183,000,000



Patients with diabetes who are **not** using insulin

$317,000,000

A1c=hemoglobin A1c **ac**=before meals **Alternate Site Testing (AST):** Most newer meters allow for testing from forearm, upper arm, palm, thigh or abdomen as well as usual fingertip, **Automatic Coding**= all meters are automatically coded unless otherwise specified **ave**=averaging **BG**=blood glucose **CADTH**=Canadian Agency for Drugs & Technologies in Health **CI**=confidence interval **COMPUS**=Canadian Optimal Medication Prescribing and Utilization Service **CV**=cardiovascular **Eng/Fre**=English and French **Exp**= Expiration **Fx(s)**= Function(s) **Glu**= glucose **IFR**=infrared data transfer **IP**=Insulin Pump **Ket**=ketones **OAHA**=oral anti-hyperglycemic agent **RCT**=randomized controlled trial **SMBG**=self-monitor blood glucose pc=after meals **T2DM**=Type 2 diabetes **TS**=Touch Screen **WMD**=weighted mean difference {ReliOn Micro & ReliOn Ultima are low strip cost options but only available at Walmart in the USA (Not in Canada) }

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Farmer AJ, Perera R, Ward A, et al. **Meta-analysis** of individual patient data in randomised trials of self monitoring of blood glucose (**SMBG**) in people with non-insulin treated type 2 diabetes. BMJ. 2012 Feb 27;344:e486. {SMBG does not appreciably improve control in T2DM patients not on insulin. ↓A1C only marginally 8.3%⇨8.05%.}
FDA Aug/10 and CDC have noted a progressive increase in the reports of bloodborne infection transmission over the past 10 to 15 years (**primarily hepatitis B virus**), resulting from shared use of fingerstick and point-of-care [POC] blood testing devices.
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.
FDA Apr/14 is advising people with diabetes and health care professionals to stop using **GenStrip Blood Glucose Test Strips** because the strips may report incorrect blood glucose levels.
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.
FDA Jan/16 Arkray is recalling the **SPOTCHEM II Basic PANEL-1 Reagent Test Strip** and SPOTCHEM II Glucose Reagent Test Strip because they may report falsely low blood glucose levels.
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Weight Loss: Online Extras

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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, 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
Lorcaserin BELVIQ **D/C b/c of cancer** 10mg tab, 20mg XR tab	PL	• Class: Serotonin 2c agonist [feels full] • USA only [schedule IV, 2012]. Weight loss: ~3 kg at 1 yr; **NNT=4**.[19] Stop at 12wks unless ↓5% wt. AE: HA, fatigue, dizzy, depression, migraine, memory lapse, ?↑BP/?**cancer** [FDA'20]/valve dx/euphoria. DI: serotonin sx with other serotonergics; inhibits CYP2D6.	10mg po BID[CAMELLIA-TIMI 61: ↔CV] 20mg XR po daily	**Withdrawn from market Feb 2020** Canada
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: take 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:** 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
Rimonabant ACOMPLIA [D/C worldwide] cannabinoid-1 receptor blocker; ↓4.7kg; 20mg/d; AE: mood Δ's 12%, drop out >45%.[37]				

Diets

Most diets have short-term (e.g. six month) results compared to usual diet, but in the long-term (e.g. after 6 months) weight is regained. See http://www.cfp.ca/content/57/8/894.full or https://www.bmj.com/content/369/bmj.m1269. Overall, there is a plethora of choice and but no clear winner. Individuals should know that reducing dietary engery intake – regardless of macronutrient compositon – will result in modest weight loss after 6 months. Instead, focus on how to best maintain any weight loss achieved. Examples of diets 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.

Some 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

Canadian Obesity Network http://www.obesitynetwork.ca/pro-home

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

Useful discussion on the pros and cons of Bariatric Surgery: www.thelancet.com/journals/landia/article/PIIS2213-8587(17)30435-7/abstract (Spittal et al. Bariatric surgery: many benefits, but emerging risks. Lancet Diabetes Endocrinol. 2018 Mar.)

ALLI	55
BELVIQ	55
Bupropion	55
CONTRAVE	55
Dieting	55
Drug-Induced Weight Gain	55
Exercise	55
Fluoxetine	55
GLUCOPHAGE	55
Herbal	55
Liraglutide	**55**
Lorcaserin	55
MERIDIA	55
Metformin	55
Obesity	55
Orlistat	55
Phentermine	55
Physical Activity	55
PROZAC	55
QSYMIA	55
SAXENDA	55
Sibutramine	55
TOPAMAX	55
Topiramate	55
Weight Loss	55
WELLBUTRIN	55
XENICAL	55
Semaglutide	**55**
OZEMPIC	55
WEGOVY	55

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Fedorka PN, Murali SB, Rajaratnam DR. **Abdominal Pain and Vomiting in a Pregnant Woman Who Has Had a Gastric Bypass Procedure**. JAMA. 2019 Feb 20.

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 2010: Orlistat n=13 severe liver injury https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm213038.htm

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.
FDA Dec/16 laboratory analysis confirmed that **Queen Slimming Soft Gel** contains sibutramine.
FDA Jan/17: **ABX Weight Loss, Ultimate Body Tox** has undeclared sibutramine.
FDA Jan/17: **Accelerator Boost** has undeclared phenolphthalein.
FDA Jan/17: **Results & Zi Su Body Fat Health II** has undeclared sibutramine and phenolphthalein.
FDA Jan/17: **Skinny Bee Diet** has undeclared desmethylsibutramine, sibutramine, and phenolphthalein.
FDA Jan/17: **Supreme Slim 5.7** has undeclared phenolphthalein and sildenafil.
FDA Feb/17 laboratory analysis confirmed that **Lean Extreme Max, Slimming Plus Advanced, Platinum Weight Solution – Fat Loss Metabolizer & X-treme Beauty Slim** contains sibutramine.
FDA Mar/17 analyzed samples of **La Bri's Body Health Atomic** and found it to contain the undeclared ingredient sibutramine.
FDA Jul/17: **EZ Weight Loss TX** is voluntarily recalling all lots of **La Bri's Body Health Atomic and Xplode capsules** to the consumer level since it was tainted with sibutramine.
FDA Aug/17 laboratory analysis confirmed that **Physic Candy – Curve & Physic Candy**-Define contains sibutramine.
FDA Oct/17 laboratory analysis confirmed that **A1 Slim** contains sibutramine and phenolphthalein.
FDA Mar/18: Bella All Natural is voluntarily recalling its **Diet Capsules labeled as Bella**, Lot Number MFD:10.15.2017 EXP: 10.14.2019, to the consumer level. This recall has been initiated due to presence of sibutramine.
FDA 2010: **Orlistat** https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm213038.htm
FDA Jul/18: laboratory analysis confirmed that **Asunsa contains sibutramine, N-desmethylsibutramine, benzylsibutramine, phenolphthalein and diclofenac**.

FDA July/18: laboratory analysis confirmed that **Lyn DTOX FS3 contains sibutramine and N-desmethylsibutramine**.
FDA Aug/18: is advising consumers **not to purchase or use Nuvitra**, a product promoted for weight loss. This product was identified during an examination of international mail shipments. FDA laboratory analysis confirmed that Nuvitra **contains sibutramine and fluoxetine**.
FDA Sep/18: laboratory analysis confirmed that Slimming Capsule contains sibutramine and phenolphthalein.
FDA Sep/18: laboratory analysis confirmed that BodySlim Herbal & Easy 2 Slim contains sibutramine.
FDA Oct/18: laboratory analysis confirmed that Green Lean Body Capsule * Baschi Quick Slimming Capsule contains sibutramine and N-desmethylsibutramine.
FDA Oct/18: laboratory analysis confirmed that Shengan Natural Model, Like Slim Coffee & In Shape contains sibutramine.
FDA Oct/18: Fat Burners Zone is voluntarily **recalling 1 lot of Zero Xtreme, capsules to the consumer level**. FDA analysis has found Zero Xtreme to be **tainted with sibutramine.**
FDA Jan/19: laboratory analysis confirmed that **Slimina contains sibutramine**.
FDA Jan/19: laboratory analysis confirmed that **GoLean Detox & Slimmer Extreme Thermogenic Formula** contains sibutramine and phenolphthalein.
FDA Jan/19: laboratory analysis confirmed that **Slim Bio Capsules** contain sibutramine, N-desmethylsibutramine, sildenafil, tadalafil, benproperine and diphenhydramine.
FDA Jan/19: laboratory analysis confirmed that **Ultra Fit, 1 Day Diet** contains sibutramine and N-desmethylsibutramine.
FDA Feb/19: **GoLean Detox Capsules by GoLean Detox USA: Recall** - Due to Presence of Undeclared Sibutramine and Phenolphthalein.Pdf Guo W, Key TJ, Reeves GK. Accelerometer compared with questionnaire measures of physical activity in relation to body size and composition: a large cross-sectional analysis of UK Biobank. BMJ Open. 2019 Jan 29;9(1):e024206.
FDA Jun/19: laboratory analysis confirmed that **Adelgasin Plus, Lishou Fuling Jiaonang & Absolute Nine Slim** contains sibutramine and N-desmethyl sibutramine.
FDA Jun/19: laboratory analysis confirmed that **Super Slimming Herb & Detoxi Slim** contains sibutramine.
FDA July/19: laboratory analysis confirmed that **Reduktis Max** contains sibutramine.
FDA Sep/19: laboratory analysis confirmed that **Love in S contains sibutramine and N-desmethylsibutramine**.
FDA Sep/19: laboratory analysis confirmed that **Sheaya Lender contains sibutramine and fluoxetine**.
FDA Oct/19: laboratory analysis confirmed that **Skinny Pill contains undeclared DMAA**, also known as 1,3-dimethylamylamine or methylhexanamine.
FDA Apr/20: continues to work with the manufacturers to evaluate reports of **deaths in patients with liquid-filled intragastric balloon systems** used to treat obesity.
FDA Nov/20: laboratory analysis confirmed that **Livtone** contains sibutramine and fluoxetine.
FDA July/21: laboratory analysis confirmed that **Genesis Ultra Slim Gold** contains sibutramine and phenolphthalein.
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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.
Health Canada Jan/17 wishes to advise Canadians that **hCG (human chorionic gonadotropin)** is not authorized or proven as a weight loss aid, and could pose serious health risks.
Health Canada Mar/17: **Queen Slimming Soft Gel** contains undeclared sibutramine
Health Canada Mar/17: VIP **Bio Mangosteen Complex** contains undeclared sibutramine & phenolphthalein.
Health Canada Mar/17: **CA NI Slim BELLANCE** has undeclared orlistat by the Hong Kong Department of Health.
Health Canada Mar/17: **Lean Extreme Max & X-treme Beauty Slim** has undeclared sibutramine by the FDA.
Health Canada Mar/17: **Platinum Max Strength Blue Pill Version, Slimming Plus Advanced & Platinum Weight Loss Solution** has undeclared sibutramine & phenolphthalein by the FDA.
Health Canada May/17: **Anyang Herbal Blue** by Singapore Health Sciences Authority has undeclared sibutramine.
Health Canada May/17: **Anyang Herbal Red** by Singapore Health Sciences Authority has undeclared diclofenac, phenolphthalein, and sibutramine.
Health Canada May/17: **Change Me Herbal Slimming Capsules & Ultimate & Herbal Slim Weight** Loss capsules by Australia Therapeutic Goods Administration has undeclared sibutramine.
Health Canada June/17: **Lose Weight capsules** has undeclared sibutramine and diclofenac by Australia Therapeutic Goods Administration.
Health Canada June/17: **Slim-Vie Slimming Capsules** has undeclared sibutramine, sildenafil, and phenolphthalein by Australia Therapeutic Goods Administration.
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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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Testosterone Drug Comparison Chart

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See also: RxFiles Sexual Dysfunction chart, RxFiles Erectile Dysfunction chart

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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 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.

FDA May/17 Genetic Edge Compounds recalled all lot codes of **GEC Laxoplex dietary supplement capsules** distributed between February 2, 2015- May 2, 2017 to the retail level and consumer level. FDA analysis found GEC Laxoplex to be tainted with anabolic steroids and steroid like substances

FDA May/17: Dynamic Technical Formulations LLC. is voluntarily recalling all lots of **Tri-Ton**. This product was sold in 90 count bottles as a dietary supplement and includes all lot number and expiration dates of the product. FDA lab analysis of Tri-Ton was found to contain andarine and ostarine which are selective androgen receptor modulators (SARMs) that are considered unapproved drugs and anabolic steroid-like substances.

FDA Jul/17: Hardcore Formulations is voluntarily recalling all lots and expiration dates of **Ultra-Sten and D-Zine** capsules to the consumer level. These products are labeled to contain methylstenbolone (Ultra-Sten) and dymethazine (D-Zine), which are considered to be derivatives of anabolic steroids.

FDA Jul/17: Andropharm is voluntarily recalling all lots of **Sten Z and M1 Alpha capsules** to the consumer level because these products **contain derivatives of anabolic steroids** rendering them unapproved drugs for which safety and efficacy have not been established and therefore subject to recall.

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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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Thyroid Disorders

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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 associated with levothyroxine treatment.

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). A **bone mineral density test** (BMD) may also be indicated (esp. in the elderly) to rule out osteoporosis.

3. Management of thyroid nodules: Do TSH & ultrasound as part of initial workup. Then:

Management is determined based on ultrasound appearance.[36] Nodules are rated as benign, not suspicious, mildly suspicious, moderately suspicious, or highly suspicious (score is based on composition, echogenicity, shape, margin, and echogenic foci of the nodule using the **ACR TI-RADS** system). Suspicion level then determines criteria for fine-needle aspiration or follow-up ultrasound.	**ACR TI-RADS Scoring System** available here

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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.

FDA Aug/18: alerts drug makers of a recall of porcine thyroid API from Sichuan Friendly Pharmaceutical Co., Limited, China was just added to the FDA Recalls webpage.

FDA May 2020: **Acella is recalling 13 lots of 30-mg, 60-mg and 90-mg NP Thyroid tablets**, because company's laboratory testing found these lots to be superpotent. The product may have up to 115.0% of the labeled amount of Liothyronine (T3).

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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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www.acponline.org/patients_families/diseases_conditions/hypothyroidism/

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IDIOPATHIC HIRSUTISM: Online Extras

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Table 2. Additional Hirsutism Agents for special indications

Class / Ingredient	Place in therapy	Mechanism of Action	Efficacy	CI	Major AEs	Dose / Cost (30d)
Prednisone (Glucocorticoid) 1, 5$, 50$mg tab; {1mg/ml prednisolone soln}	- Classic & Nonclassic congenital adrenal hyperplasia (CAH)	-Suppresses adrenal function	-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 $12 (5mg tab)
Ketoconazole NIZORAL 200$mg tab ☎▼	- For patients with Cushing's syndrome while waiting definite therapy *Only for use by specialists – can cause life threatening adrenal crisis*	-Adrenal enzyme inhibitor	-Similar efficacy to CPA 2-50mg[20]	Hepatic dysfunction Pregnancy, BF	- Gynecomastia, dry skin, **hepatotoxicity**, adrenocortical suppression	200mg po daily $41 (200mg tab)
Leuprolide Acetate (GnRH analog) LUPRON(SC): Vial 5mg/ml✗⊗ LUORON DEPOT (IM)☎▼: 3.75, 7.5, 11.25, 22.5✗, 30✗ mg ELIGARD (SC)✗▼: 7.5, 22.5, 30, 45mg	- Severe hyperandrogenism of ovarian origin that does not respond to other drugs	- Potent inhibitor of ovarian steroidogenesis by suppressing LH & FSH	-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 + $24-30
MetFORMIN GLUCOPHAGE 500$, 850mg tab	- Used in polycystic ovary syndrome (PCOS). - - Not effective for idiopathic hirsutism	- improves insulin sensitivity	-Small benefit compared to placebo -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) $3-21 (500mg tab)

ALDACTONE	59
ANDROCUR	59
BCP	59
Cyproterone	59
DIANE-35	59
Eflornithine	59
Finasteride	59
Flutamide	59
Hair	59
Hirsutism	59
Metformin	59
OCP	59
PCOS	59
PROSCAR	59
Spironolactone	59
TRI-CYCLEN	59
VANIQA	59
YASMIN	59
YAZ	59
Drug-Induced Hirsutism	59

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OTHER PRODUCTS

- **Sodium phosphate** FLEET PHOSPHO-SODA, **PHOSLAX**: Not recommended due to safety concerns (electrolyte changes, dehydration, renal failure).
- **Enemas**: does not improve quality of bowel preparations & are not routinely recommended. Role in patients who present for colonoscopy with poor preparation.
- **Prokinetics**: metoclopramide, domperidone, cisapride and tegaserod did not improve the tolerability of bowel preparations or the quality of bowel cleansing.
- **Senna SENOKOT**: used as an adjunct to PEG regimens in a manner similar to bisacodyl. Senna high dose **X-PREP** used alone less effective & tolerable than low-volume PEG.
- **Simethicone OVOL**: 120-240mg po with HS & AM dose of bowel preparation to reduce bubbles & improve visualization during colonoscopy, uncertain if improves lesion detection.
- **Castor/Olive Oil**: not recommended or routinely used as adjunctive agent
- **Not Available in Canada,** 🇺🇸: Sulfate-free PEG **NULYTELY, TRILYTE** developed to avoid "rotten egg" smell & improve salty taste of PEG. **PLENVU** is a low-volume PEG-based that only requires 1 L of water for dissolution and ingestion of 1 L of clear fluid in addition. **MIRALAX** is a low-volume PEG-based that is more palatable than traditional PEG plus electrolyte solution but may be less effective than a 4-L PEG-based preparation. Dose 240mL q10 min until 1L consumed PM before procedure, repeat in AM. **SUTAB** FDA 2020 (sodium sulfate, magnesium sulfate, potassium chloride) tablets for oral use in adults. Dose 1 (12 tabs) PM before colonoscopy and Dose 2 (12 tabs) the AM of colonoscopy; each dose with 48 oz water. **SUPREP** (sodium sulfate, magnesium sulfate, potassium sulfate) liquid for oral use in adults. Dose 1 bottle (6oz) diluted in water to 16 oz, plus additional 32 oz water PM before colonoscopy and repeat in AM. **OSMOPREP** (sodium phosphate) tablets for oral use in adults. Dose 1 (20 tabs) PM before colonoscopy (4 tablets + 8oz clear liquids q15 min - total of 20 tabs); Dose 2 (12 tabs) 3-5 hrs before colonoscopy (4 tabs + 8oz clear liquids q15min - total of 12 tabs).

SPECIAL POPULATIONS

- **Pediatrics: Few studies. Compliance is an obstacle. No one size fits all. Consult with specialist.**
  - Sodium picosulfate/magnesium oxide/citric acid (e.g. **PICO-SALAX**): **1 day before procedure (start ~4-6pm), prepare solution by** mixing one sachet in 5oz cold water. **Give 1st dose as follows: 1-6yrs= ¼ of prepared solution, 6-12yrs= ½ of prepared solution, &** follow dose with one 8 oz glass of clear liquid each hour until bedtime. Keep NPO after 6pm. **Repeat same dose on day of colonoscopy at 8am** & follow with one 8 oz glass of clear liquid every hour. Stop clear fluids 2 hours prior to procedure.
  - PEG 3350 with electrolyte (e.g. **GOLYTELY**) 100mL/yr of age/hour or 20ml/kg/hr up to 1L/hr, up to 4hrs given po/NG tube until rectal effluent is clear (e.g. 800mL/hr for an 8 year old until rectal effluent is clear or max 4hrs intake of PEG). Another better tolerated approach is giving the same volume (80ml/kg) consumed over entire day before procedure.
    Adolescents: 240mL po q10min until rectal effluent is clear. Disadvantage: high volume, poor palatability. Off-label for children in Canada but has been used in pediatric studies.
  - PEG 3350 without electrolytes (e.g. **LAX-A-DAY**) 1.5-2g/kg/day (max 136g/d) +/- bisacodyl 5mg/day x both for 2 days, the last day of which child is maintained on clear liquids. Mild, well tolerated & relatively simple to administer. 1 day regimen: <45kg -136g PEG without electrolytes in 32 oz Gatorade (or similar sports drink), ≥45kg 255g PEG without electrolytes in 64oz Gatorade. Potential concerns when mixed with sports drinks are hydration & electrolyte imbalances. Off-label for pediatric use in Canada.
  - Pediatric **FLEET** enemas & high-dose senna **X-PREP** is a less favoured option.
- **Pregnancy:** full colonoscopy rarely indicated during pregnancy. Tapwater enemas are recommended as bowel preparation for sigmoidoscopy. If total colonoscopy required, PEG regimens may be considered. PEG has not been studied in pregnancy & unknown if it can cause fetal harm; considered relatively safe to treat constipation in pregnancy (↓ dose).
- **Breastfeeding:** No reported information. Interrupting breastfeeding during and after bowel preparation may be an option.
- **Diabetes:** People with DM have inadequate bowel preparation more often than people without DM and frequently require a subsequent colonoscopy possibly due to colon dysmotility (diabetic neuropathy), ↓ physical activity, and/or meds that slow bowel motility (e.g. calcium antagonists).
  - PEG bowel cleansing solution preferred (less risk of kidney injury and electrolyte imbalance compared to other options). • Frequently monitor blood glucose the day before and day of procedure
  - Prior to colonoscopy: low fibre or clear liquid diet with 45-60 g carbohydrates at meals, drink clear sugar-free fluids between meals↓ risk of dehydration, nothing by mouth 2-12 hours prior to procedure.
  - **Medications:** Day before procedure: Stop SGLT-2 inhibitors ("flozins"), sulfonylureas, meglitinides. Stop other oral antihyperglycemics when no longer eating solid foods (e.g. metformin, DPP4-inhibitors ("gliptins"), GLP-1 receptor agonists (e.g., liraglutide). Hold ACEI/ARB at the time of colonoscopy. Individualize insulin dose accordingly. Resume meds once solid foods are reintroduced.

LOW RESIDUE DIET - NO ALCOHOLIC BEVERAGES 24 HOURS PRIOR TO PROCEDURE

Started 24-48 hours prior to colonoscopy, changing at midnight the day prior to colonoscopy to clear fluid until 2 hours before colonoscopy (e.g. water, apple juice, white cranberry juice, white grape juice, soup broth, clear sodas, sport drinks, coffee/tea without cream/whitener, popsicles, gelatin desserts; avoid flavours/drinks with red & purple colors as these can discolour the lining of the bowel).

FOODS TO AVOID	FOODS ALLOWED
Yogurt or cheese with fruits or seeds	All milk & milk products, except those outlined in the Foods to Avoid column
Whole grains, bran, bran cereals, brown/wild rice, whole wheat flour, rich cookies, baked goods/candies/or pastry made with nuts, seeds, coconut, dried fruit or berries, popcorn	Refined white bread, pasta, white rice, refined cereal, soda crackers
Processed or spiced meat, sausages, tough meats, chunky peanut butter, dried peas, beans, lentils, lima beans, nuts/seeds, shrimp	Eggs, most tender meats (skinless), soft casseroles, smooth peanut butter/hummus
Berries, cherries, currents, dates, grapes, kiwi, orange pulp, prunes, prune juice, raw pineapple, raisins, rhubarb, all dried fruit, unpeeled raw fruit, fruit with seeds, fruit cocktail	Soft fruits/peeled melon, canned fruit without skins, baked fruit/applesauce. Fruit juice without pulp
Fried, hard cooked or raw vegetables, bamboo shoots, bean sprouts, broccoli, brussel sprouts, cabbage, carrots, cauliflower, celery, coleslaw, corn, cucumber, lettuce, mushrooms, onions, peppers, pea pods, radishes, sauerkraut, spinach, tomatoes	Well cooked vegetables (green beans, skinless potatoes, skinless and seedless tomato sauce, tomato paste, turnips), vegetable juice, spaghetti sauce
	Mild herb/spices, salt/pepper, ketchup, mustard, BBQ sauce, mayo, butter, oil
Soups made with dried peas, beans, lentils, peas, spices	Plain broth, bland strained cream soup

▼=covered by NIHB **ACEI**=angiotensin converting enzyme inhibitor **AE**=adverse events **ARB**=angiotensin receptor blocker **CI**=contraindications **CKD**=chronic kidney disease **CrCl**=creatinine clearance **DI**=drug interactions **DM**=diabetes mellitus **dx**=disease **g**=generic **GI**=gastrointestinal **H_2O**=water **HF**=heart failure **hrs**=hours **IBD**=irritable bowel disease **L**=litre **Mg^{++}**=magnesium **Na^+**=sodium **NG**=nasogastric **NPO**=nothing by mouth **oz**=ounce **PEG**=polyethylene glycol **po**=orally **pr**=per rectum **pt**=patient **SBP**=systolic blood pressure **SIADH**=syndrome of inappropriate antidiuretic hormone secretion **tx**=treatment

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Split-dose Regimen	60
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RxFiles Management of Constipation On-Line Extras:

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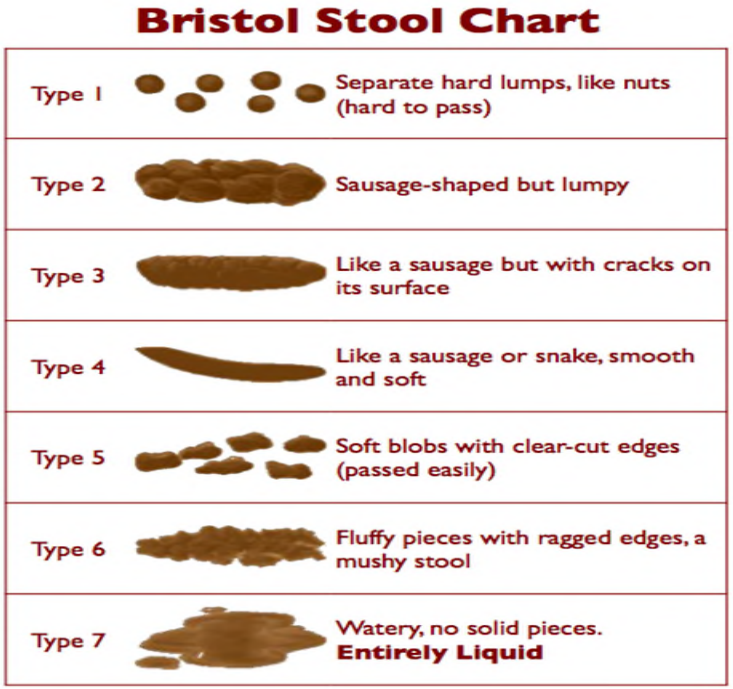
The Bristol Stool Chart: a validated tool to correlate stool consistency with colonic transit time. Use with patients for assessment & monitoring.



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FDA Jan/18 Magno-Humphries Laboratories, Inc., is voluntarily **recalling** one lot of **Basic Drugs Brand of Senna Laxative tablets**, 8.6mg Sennosides to the consumer level due to a customer complaint that their bottle labeled as Senna Laxative actually contained Basic Drugs Brand of Naproxen Sodium 220mg.

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Health Canada Jul/17 is advising Canadians that Bayer Inc. is voluntarily recalling **RestoraLAX 45 + 10** Value Pack sold at Costco Canada due to a potential **choking hazard**. The recalled product may contain deposits such as clumps or lumps. The presence of these deposits may pose a choking hazard.

Health Canada Jul/17 is advising Canadians that Bayer Inc. is expanding its voluntary recall to include specific lots of **RestoraLAX 30+7 B**onus Packs sold at various retailers across Canada due to a potential **choking hazard**.

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Cochrane reviews CD:

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

Cochrane reviews UC:

- 5-ASA superior to placebo to induce remission in UC & trended towards benefit over sulfasalazine (SSZ). However, cost an issue, therefore SSZ generally preferred. 5-ASA has fewer SE than SSZ. 5-ASA not associated with male infertility, but SSZ is.
- 5-ASA superior to placebo in maintaining remission for UC (NNT=6). 5-ASA NOT superior to SSZ (NNT= -19), indicating SSZ superior. HOWEVER, many trials required tolerance of SSZ as part of inclusion criteria (Bergman 2006)
- Transdermal nicotine superior to placebo for inducing remission in UC, however no benefit was seen when compared to standard therapy (oral prednisone or mesalamine). More patients on transdermal nicotine withdrew due to AE then placebo or standard therapy.
- Only 2 small trials identified for CsA; could not be pooled as major differences in design & patients involved. Quick response rates in severe disease appear beneficial, but long-term effects unknown.
- In moderate-severe, refractory disease, infliximab induces remission. NNT=5 at 8 weeks (based on ACT studies alone)
- 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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- **Guidelines:** Nguyen GC, Seow CH, Maxwell C, et al; IBD in Pregnancy Consensus Group. Canadian Association of Gastroenterology. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy. Gastroenterology. 2016 Mar;150(3):734-757.e1.
    - TNF-α inhibitors: Consider D/C 22-24wks gestation if ↓ relapse risk (e.g. sustained remission durring the 12 months before conception, no active disease on endoscopy or imaging during the preconception period, no prior secondary loss of response to anti-TNF therapy or dose escaltion, demonstrated therapeutic levels of anti-TNF therapy, no prior intestinal resections, and no hospitalizations in the past 36 months).
- IBD Patient Information- Pregnancy (University of Saskatchewan Multidisciplinary Inflammatory Bowel Disease Clinic): http://mdibdc.com/images/userImages/files/IBD%20and%20Pregnancy%20Module.pdf

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***Helicobacter Pylori* Eradication**

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RxFiles: Acid Suppression Chart On-Line Extras

Complete List of Abbreviations

2°=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**=acetylsalicylic 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	-

Acid Suppression	70
ACIPHEX	70
AXID	70
Cimetidine	70
DEXILANT	70
Dexlansoprazole	70
Drug-Induced GERD	70
Esomeprazole	70
Famotidine	70
Histamine 2 Receptor Antagonist	70
KAPIDEX	70
Lansoprazole	70
LOSEC	70
NEXIUM	70
Nizatidine	70
Omeprazole	70
PANTOLOC	70
Pantoprazole	70
PARIET	70
PEPCID	70
PPI	70
PREVACID	70
Ranitidine	**70**
TAGAMET	70
TECTA	70
VIMOVO	70
ZANTAC	**70**
Gastric Ulcer	**70**
Ulcer	**70**
Peptic Ulcer Disease	**70**
Gastroprotection	**70**

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FDA Mar/11 Proton Pump Inhibitor drugs (PPIs): Drug Safety Communication - **Low Magnesium Levels** Can Be Associated With Long-Term Use.
FDA Apr/11: Teva's lansoprazole **delayed-release orally disintegrating tablet has clogged** and blocked oral syringes and feeding tubes, including both gastric and jejunostomy types, when administered as a suspension.
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.
FDA Sep/19 has learned that some **ranitidine medicines**, including some products commonly known as the brand-name drug **Zantac**, contain a nitrosamine impurity called N-nitrosodimethylamine (NDMA) at low levels.
FDA Oct/19: Dr. Reddy's Laboratories Ltd. intiatiated a voluntary nationwide **recall of all of its ranitidine** medications sold in U.S. due to confirmed contamination with N-Nitrosodimethylamine above levels established by the FDA.
FDA Oct/19: says that **alternatives to over-the-counter ranitidine** don't appear to contain the same potentially carcinogenic substance as ranitidine. Several lots of OTC ranitidine have been recalled because of the presence of small amounts of N-nitrosodimethylamine (NDMA), a probable human carcinogen. The most recent recalls include all brand name OTC Zantac, as well as some generic products labeled by

Walgreens, Walmart, CVS, Target, and Kroger. Meanwhile, preliminary tests haven't detected NDMA in other heartburn medications, including famotidine (Pepcid), cimetidine (Tagamet), esomeprazole (Nexium), lansoprazole (Prevacid), or omeprazole (Prilosec).

FDA Oct/19 Lannett Company, Inc. today announced that it is voluntarily **recalling all lots within expiry of Ranitidine Syrup** (Ranitidine Oral Solution, USP), 15mg/mL to the consumer level due to levels of N-Nitrosodimethylamine (NDMA) above the levels recently established by the FDA for Ranitidine Hydrochloride Syrup (Ranitidine Oral Solution, USP).

FDA Oct/19: **Ranitidine Syrup**, 15 mg/mL (Ranitidine Oral Solution USP) by Lannett: Recall - Due to Levels of N-Nitrosodimethylamine (NDMA) above the Levels Recently Established by the FDA

FDA Nov/19: Drugmakers may be **recalling the heartburn med Zantac** around the world, but the FDA wants consumers to stop worrying. Higher-than-recommended levels of a possible carcinogen in the pills are no more dangerous than a grilled ribeye, the agency said Monday. Testing of recalled lots of branded and generic Zantac showed levels of a contaminant known as N-Nitrosodimethylamine (NDMA) that were as much as nine times greater than the FDA's recommended limit—but the agency pooh-poohed the health risk in a release.

FDA Nov/19 Levels of N-nitrosodimethylamine **(NDMA) in many tested ranitidine products** are similar to those consumed through "common foods like grilled or smoked meats," the FDA said on Friday.

FDA Nov/19: Aurobindo Pharma USA: **Recall: 38 Lots of Ranitidine** Tablets, Ranitidine Capsules and Ranitidine Syrup by Aurobindo Pharma USA: Recall - Due to the Detection of Nitrosodimethylamine Impurity. Ranitidine Syrup, 150 mg/10 mL (Ranitidine Oral Solution USP) by American Health Packaging: Recall - Due to the Detection of N-nitrosodimethylamine (NDMA) Impurity.

FDA Nov/19: **Ranitidine Capsules** by Golden State Medical Supply: Recall - Due to an Elevated Amount of Unexpected Impurity, N-Nitrosodimethylamine (NDMA).

FDA Dec/19: Over the past several weeks, FDA has communicated about the detection of an impurity known as N-nitrosodimethylamine **(NDMA**) in common heartburn medications (**ranitidine**, commonly known as **Zantac, and nizatidine**) available over the counter or by prescription.

FDA Jan/20: **Ranitidine** Hydrochloride Capsules by Appco Pharma: Recall - Due to an Elevated Amount of Unexpected Impurity, N-Nitrosodimethylamine.
Nizatidine Capsules by Mylan: Recall - Due to Detected Trace Amounts of NDMA Impurity Found in the Active Pharmaceutical Ingredient

FDA Apr/20: announced it is requesting manufacturers to **withdraw all** prescription and over-the-counter (OTC) **ranitidine drugs** from the market immediately.

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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.

Health Canada Apr/13 is informing Canadians and Canadian health care professionals of the potential risk of **bone fractures** associated with the use of drugs known as **proton pump inhibitors**.

Health Canada Sep/19 is informing Canadians that it is aware that the impurity N-nitrosodimethylamine (NDMA) has been detected in some ranitidine drugs.

Health Canada Sep/19: recently informed Canadians that it is assessing the issue of an impurity called N-nitrosodimethylamine (**NDMA) detected in some ranitidine drugs**. Current evidence suggests that NDMA may be present in ranitidine, regardless of the manufacturer. As a result, and at Health Canada's request, companies marketing ranitidine products in Canada have stopped any further distribution until evidence is provided to demonstrate that they do not contain NDMA above acceptable levels.

Health Canada Sep/19 **requests that companies stop distributing ranitidine** drugs in Canada while it assesses NDMA; additional products being recalled.

Health Canada Nov/19: has been working to address the issue of N-nitrosodimethylamine (NDMA) and similar nitrosamine impurities found in certain "sartan" angiotensin receptor blocker (ARB) blood pressure medications since 2018 and, certain ranitidine drugs more recently.

Health Canada Apr/20: Pendopharm Division of Pharmascience Inc. is recalling two lots (616927 and 617088) of Axid (**nizatidine**) from the Canadian market, as they contain a nitrosamine impurity, N-nitrosodimethylamine (NDMA), which is a probable human carcinogen, at the maximum acceptable limit.

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RxFILES: HELICOBACTER PYLORI TESTING & ERADICATION

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

Extras &/or Historical Note

Quadruple 1 day regimen: PPI double dose + bismuth 2 tab QID + metronidazole 500mg QID + amoxicillin 2gm QID[10]

Acid Suppression	71
ACIPHEX	71
DEXILANT	71
Dexlansoprazole	71
Esomeprazole	71
H. Pylori	71
Hp-PAC	71
KAPIDEX	71
Lansoprazole	71
LOSEC	71
LOSEC 1-2-3-M	71
NEXIUM	71
Omeprazole	71
PANTOLOC	71
Pantoprazole	71
PARIET	71
PPI	71
PREVACID	71
Pylori	71
TECTA	71
Gastric Ulcer	**71**
Ulcer	**71**

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Online Extras: IRRITABLE BOWEL SYNDROME (IBS)

Legend
ς =scored tablet χ =Non-formulary SK ☎=EDS in SK ✆=prior approval NIHB ⊗=not NIHB ▼=covered NIHB ☖= NIHB Palliative Care Formulary **BBB**=blood brain barrier **BP**=blood pressure **CBT**=cognitive behaviour therapy **CD**=Crohn's disease **CIC**=chronic idiopathic constipation **CV**=cardiovascular **D**=diarrhea **FIT**=fecal immunochemical test **FMT**=fecal microbiota transplantation **hx**=history **IBD**=irritable bowel disease **mo**=months **N**=nausea **NEH3**=sodium/hydrogen exchanger 3 **NNT/H**=number needed to treat/harm **SJW**=St. John's Wort **sx**=symptom **UC**=ulcerative colitis **V**=vomiting

General Treatment Approach

- Develop a trusted clinician-patient relationship is a cornerstone of effective therapy. Engage in active listening, empathy and setting realistic expectations.
- Treatment goals aim to resolve symptoms and encourage living well with IBS
- An interprofessional approach will help to improve quality of life, avoid over-reliance on medications and allow for better symptom management.

Lifestyle Interventions:

- Journal to track triggers
- Diet low in FODMAPS
  - 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
- Increase soluble fibre (oat bran, psyllium, etc.)
- Behavioral Therapies for IBS along with medical therapies, may help reduce pain and improve satisfaction with bowel habits when there is concomitant stress, hyperarousal, anxiety, fear, or maladaptive thoughts drive symptoms. Examples of behavioral therapies include: Gastrointestinal Cognitive Behavior Therapy (relaxation training, cognitive reframing including catastrophizing, behavioral/emotional/interoceptive exposure), gut-directed hypnotherapy, mindfulness-based stress reduction, and psychodynamic interpersonal psychotherapy

Differential Diagnosis: IBD Ulcerative/Microscopic colitis, Crohn's, colorectal polyp/cancer, malabsorption lactose intolerance, celiac dx, pancreatic insufficiency, infectious diarrhea giardia, bacteria, traveller's, thyroid, gyne or mental health depression, anxiety
To help exclude other dx: antibody testing for celiac disease, CBC, *C. difficile* for diarrheal stools, & CRP or ESR NICE 2015, AGA 2019 **Other optional tests**: TSH; Stool occult blood/ova/parasites Mayer'08; calprotectin fecal, FIT test, , IBSchek?
Opioids: Most suggest to avoid due to AEs, substance use disorder risk, & lack of evidence in IBS.[13] Option in select pain pts. If diarrhea, may not absorb SR formulations.

Discontinued Drugs: **Alosetron** LOTRONEX (2000 -severe constipation & ischemic colitis) 0.5-1mg bid, for women only. Not avail. in Canada.

Tegaserod **ZELNORM**: Mar07- suspended due to CV ischemic events; but Apr08-FDA for Emergency IND situations only use in IBS-constipation & chronic idiopathic constipation in ♀<55yr with no hx of heart problems. 6 mg po bid $160 (NNT=14) 5HT4 agonist
Not avail in Canada. Oct/18: FDA panel agrees to approve. **Apr/19: FDA approved for women <65yrs with IBS-C, but CI: if history of MI, stroke, TIA or angina**.

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

Probiotics: Low quality evidence, IBS: **ALIGN**, **HMF FORTE**, **PREGNANCY CARE PROBIOTIC**, **ULTRAFLOR BALANCE**; IBS-C: **ACTIVIA**, **TUZEN**, **ULTRAFLORA**; IBS-D: **BIO-K+**

Patient Info/Video NICE IBS Information for the public, Low FODMAP Diet, Canadian Society of Intestinal Research IBS Videos, Canadian Digestive Health Foundation IBS Animation

FMT: Fecal Microbiota Transplantation restore the gut endocrine cells to the level of healthy subjects.

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.

Considerations:

-Study of 215 ER patients randomized to 1.25mg of IV droperidol vs. 8mg of IV ondansetron vs. placebo. Both antiemetics reduced nausea similarly to placebo. However, this study was stopped early and more patient centered metrics such as "experienced desired effect" and need for rescue medications were lower than in the placebo group (ondansetron > droperidol > placebo)[38]

-Evidence for Isopropyl alcohol: "Two trials with about 200 nonpregnant adults presenting to the ED found inhaled (smelling) isopropyl alcohol improved mild to moderate nausea and vomiting. For example, after 30 minutes the nausea score improved from 50 out of 100 to 20 with inhaled isopropyl alcohol versus 40 with oral ondansetron. Only 1 study reported adverse events and found none."[39]

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 hyperemesis gravidarum likely affects <1%
- Tx: fluids & electrolytes, thiamine (or IV if prolonged & unable to take po), antiemetics. Reserve corticosteroids for severe/refractory cases (limited evidence, conflicting efficacy e.g., re-hospitalizations).

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Droperidol INAPSINE 5mg/2ml amp (FDA only now)	0.625-2.5mg IM/IV slow; ?ECG prior $8/amp ✗ ⊗	As above (esp. akathisia); ↑QT ? interval & sudden death (controversial) [19]

Other Links:

Info SOGC: https://www.pregnancyinfo.ca/your-pregnancy/healthy-pregnancy/nausea-and-vomiting/
HER(hyperemesis-gravidarum): http://helpher.org/hyperemesis-gravidarum/
CFP Motherisk: http://www.cfp.ca/cgi/reprint/53/12/2109.pdf.
N/V Links: AFP PONV Prediction: http://www.aafp.org/afp/20070515/poc.html
AFP Evaluation n&v: http://www.aafp.org/afp/20070701/76.html
Australia FP: http://www.racgp.org.au/afp/200709

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References for NAUSEA & VOMITING: Drug Treatment Options:

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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
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 Jan/18: Anaphylaxis, anaphylactic shock and other serious **hypersensitivity reactions** have been reported in the postmarketing setting, some requiring hospitalization. These reactions have occurred during or soon after the infusion of Varubi (**rolapitant**) injectable emulsion. Most reactions have occurred within the first few minutes of administration. Symptoms of anaphylaxis can include wheezing or difficulty breathing; swelling of the face or throat; hives or flushing; itching; abdominal cramping, abdominal pain or vomiting; back pain or chest pain; hypotension or shock.
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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**.
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Online Extras: **Erectile Dysfunction**

Table 4. Penile injections and urethral suppositories.

Generic/TRADE	Class	Adverse Events AE / Contraindications CI	✓official indications / Comments / Drug Interactions DI / Monitor M	Initial; Max; Usual Dose	$ /4 doses
Alprostadil PL **CAVERJECT** ✗ ⊗ 20 ug vial (powder) **Intracavernosal inj.** **MUSE** ✗ ⊗ 250, 500, 1000 ug **Urethral supp** **Prostaglandin= E1** **inj** corpora cavernosa; transurethral **gel**	**Prostaglandin E** - ↑'s production of cAMP which relaxes smooth muscle and produces vasodilation - Also inhibition of platelet aggregation and gastric secretion, stimulation of intestinal smooth muscle, uterine smooth muscle - Most efficacious of injectable agents	- **Common AE**: ↓ HR[7%], dizziness, fever[14%], headache, hypotension[4%], penile pain[37%], penile fibrosis[3%], tachycardia[3%], urethral burning, vaginal itch (in partner with transurethral systems) - **Serious AE**: seizures[4%], priapism* [<4%], HF, second degree heart block, supraventricular tachycardia, ventricular fibrillation[<1%], disseminated intravascular coagulation[1%] & cortical proliferation of long bones - **CI**: anatomical penis deformation, penile implant, predisposition to priapism* (sickle cell anemia or trait, leukemia, myeloma), Peyronie's disease - **Precautions:** concurrent anticoagulant, vasoactive agents or bleeding abnormalities [neonates with bleeding tendency apnea possible]	✓vasculogenic, psychogenic, neurogenic, & mixed ED - **Onset** = rapid (usually within 10min) **Duration**= <1hr.[45] - Initial dosage/titration should occur under medical supervision (due to risk of syncope). Pts receiving intracavernosal inj should be re-assessed q12months. - **Vascular ED requires larger doses (>20ug) vs neurogenic ED (2-5ug)** - Injection: no more than 3 doses/week (with 24 hours between doses) - Suppositories: no more than 2 within 24 hours - ↓dose if erection lasts greater than one hour with either system - Seek medical assistance if tx results in erection that lasts >4 hr. **DI**: heparin (↑partial thromboplastin time & thrombin time); ↑risk of symptomatic hypotension, syncope with vasodilators, antihypertensives, alcohol **M**: *priapism (erection lasting >4hr) tx=needle aspiration of penile blood; intracavernosal inj phenylephrine 200ug q5-10min up to 1000ug if needed) - Muse refrigerate; otherwise 14 days at RT	**Neurogenic ED**: Titrate from 1 ug Usual: 2-5ug **Vascular ED**: Titrate from 4ug Usual: 5-20ug Severe: 40-60ug Inject 10-30mins pre-sex **Initial**: 125-250ug; **Max**:1000ug x1/24h **Usual**: 250-500ug 10-30mins pre-sex (dose depends on venous anatomy not ED etiology)	For 4 doses: $155 CAVERJECT $250 MUSE
Papaverine= Pv 32.5mg/ml inj. soln ✗ ⊗ (2ml vials) PL t½= 0.5-2hr	**Vasodilator** - Non-selective PDE 2,3,4 inhib - Produces generalized arteriolar dilation & smooth muscle relaxation - Can be combined with prostaglandin &/or phentolamine	- **Common AE**: abdominal discomfort, anorexia, constipation, N/V/D, drowsiness, headache, vertigo, HTN, tachycardia, pruritis, rash & blurred vision? - **Serious AE**: acidosis, ↑intercranial pressure, hepatotoxicity & priapism* - **CI**: complete atrioventricular block - **Precautions:** glaucoma, liver dx, recent MI, stroke, Parkinsonism & sickle cell anemia	✓idiopathic, postencephalitic, & symptomatic (not FDA indication) ED - **Onset** = rapid (usually within 10min) **Duration**= <1hr.[45] - Papaverine in any ischemic type condition is not recommended. - Do not use more than 3 times weekly or 2 days in succession. - Combos: Three drug combination (**Pt** + **Pv** + **E1**) up to 73% effective.[44] - Consult prescriber if erection lasts more than 4 hours after self inj **DI**: levodopa (↓ levodopa affect), ginkgo (↑ AE of papaverine) **M**: intraocular pressure in glaucoma patients, liver fx	**Initial**: 30 mg **Max**: 60mg **Usual**: 30mg-60mg intracavernosal over 1-2 min	$13 $17 $13-17 $130 /10x2mL vials
Phentolamine= Pt Rogitine, g ✗ ⊗ PL 5mg/ml vial inj **ORAVERSE** ✗ ⊗ 0.4mg/1.7ml intraoral submucosal inj	**Alpha-Adrenergic Blocker** - Antagonizes anti-erectile sympathetic tone, ↑perfusion - Poor efficacy alone so usually combined with prostaglandin &/or papaverine	- **Common AE**: chest pain, diarrhea, dizziness[3%], headache[3%], hypotension[2%], nasal congestion[10%], nausea, palpitations[1%], ↑HR[1-7%] & vomiting - **Serious AE**: arrhythmia - **CI**: myocardial infarction, CAD, angina pectoris, hypersensitivity to phentolamine or mannitol, renal impairment, coronary or cerebral arteriosclerosis - **Precautions:** arrhythmia, cerebral vascular spasm or occlusion, hypertension, ↑HR	✓idiopathic, postencephalitic & symptomatic (not FDA indication) ED - **Peak** = 30-60min **Onset** = 30-40min **Duration** = 5-7hr - Compounded mixes may ↑ efficacy and ↓ pain associated with prostaglandin - **As an adulterant in**: **DESIRE** natural product **DI**: **↑ hypotension**: ß-blockers, tadalafil & vardenafil; disulfiram like rx with alcohol; ↓ effect with ephedrine (OTC cough/cold products, diet & "wake up"pills) **M**: blood pressure changes, HR	**Compounded Products** **Bi-mix inj = Pt + Pv** 6ml vial = $63 0.5-1ml/dose **Tri-Mix inj =Pt + Pv + E1** **in 3 strengths** $110 per 5ml vial 0.2-1mL per dose **TriMix also available in Transurethral gel** $43-123 / 5x1ml syr 0.5-1ml per dose	

Table 5. Apomorphine.

Generic/TRADE	Class	Adverse Events AE / Contraindications CI	✓official indications / Comments / Drug Interactions DI / Monitor M	Dose	$ /4 doses
Apomorphine PL 2,3mg CR sublingual tabs **ApoKyn** (USA)	Centrally acting agent stimulates dopamine sites in the hypothalamus	SE: nausea (↓with time, CR SL tabs);headache, dizziness, sedation, yawning Not affected by food or alcohol	Onset <30min Peak ~1hr Duration ~1-2hr 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	**Initial**: 2-3mg SL prn **Max**: 6mg SL prn	**Discontinued in Canada**

Table 6. Etiologies of erectile dysfunction.[5,54]

Vascular	e.g. cigarette smoking, obesity, CVD, hypertension, diabetes, metabolic syndrome, lack of physical activity.
Neurological	e.g. Parkinson's, multiple sclerosis, Alzheimer's disease, stroke, spinal cord trauma, diabetes, penile or urethral surgery.
Hormonal	e.g. hypogonadism, hyperprolactinemia, hyperthyroidism, hypothyroidism.
Cavernosal	e.g. Peyronie's disease, penile fracture, cavernous fibrosis.
Drug-Induced	e.g. acetazolamide, alcohol, amiodarone, barbiturates, beta-blockers, CBZ, cimetidine, clonidine, cocaine, cyproterone, digoxin, diuretics (e.g. spironolactone, thiazides), finasteride, flutamide, ketoconazole, lithium, MAOI, marijuana, methyldopa, methotrexate, opioids, phenytoin, phenothiazine, SSRI, TCA.
Psychogenic	e.g. performance anxiety, past trauma, strict upbringing, inadequate sexual education, mental health problems, relationship problems, family or social pressures, major life events (e.g. pregnancy, childbirth, loss of a job), anxiety, depression.

Erectile Dysfunction

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ADCIRCA	75
Alprostadil	75
Avanafil	75
CAVERJECT	75
CIALIS	75
Drug-Induced Erectile Dysfunction	75
Erectile Dysfunction	75
LEVITRA	75
MUSE	75
Papaverine	75
Phentolamine	75
Phosphodiesterase 5 Inhibitor (PDE5 Inhibitor)	75
REVATIO	75
Sildenafil	75
STAXYN	75
STENDRA	75
Tadalafil	75
Vardenafil	75
VIAGRA	75
Sexual Dysfunction	**75**
Ejaculation Disorder	**75**

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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 007c**ontains 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 **Love4Long** 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.
FDA Dec/16 laboratory analysis confirmed that **Triple Green Capsules, Rhino 9 Premium 3500, Rhino 8 Platinum 8000, Rhino 7K 9000 Male Performance Booster, Duramaxxx, Rhino 5 1500, Lang Yi Hao, Bl4ck 4K capsules, Big Penis Male Sexual Stimulant, Power Male Sexual Stimulant, 90° Jiushidu capsules, Black Mamba 2 Premium, Black 3K Plus Male Sexual Enhancement Capsules & African Viagra** contains sildenafil.
FDA Jan/17: **Supreme Slim 5.7** has undeclared phenolphthalein and sildenafil.
FDA Jan/17: **Ready Man!** Has undeclared sildenafil.
FDA Feb/17 laboratory analysis confirmed that **Goldreallas XXX, Goldreallas Original, Ginseng for Reinforcing Kidney, Old Chinese, & Shenjingpian** contains sildenafil.
FDA Mar/17 laboratory analysis confirmed that **Arouse-Plus** contains tadalafil.
FDA Mar/17 laboratory analysis confirmed that **Bazook Bullet** contains aminotadalafil.
FDA Mar/17 **A&H Focal Inc**. is voluntarily recalling all lots marketed as dietary supplements for male sexual enhancement from January 2014 to present. These products have been historically tested by the FDA and found to contain PDE-5 Inhibitors (i.e.sildenafil, tadalafil, vardenafil, etc.).
FDA Apr/17 Organic Herbal Supply Supplement Products: Recall - Undeclared Drug Ingredients: Including **Uproar, Cummor, Zrect, LabidaMAX, Monkey Business, Xrect, Rectalis, Tornado, Zdaily, BigNHard, Enhancerol Natural Male Enhancement capsules-** found the products to contain Tadalafil.
FDA May/17 laboratory analysis confirmed that Big N Hard contains tadalafil.
FDA May/17 laboratory analysis confirmed that **Cummor & Monkey Business** contains N-desmethyl tadalafil.
FDA May/17 laboratory analysis confirmed that **Xrect** contains tadalafil and descarbonsildenafil.
FDA May/17 laboratory analysis confirmed that **Tornado** contains nortadalafil.
FDA May/17 laboratory analysis confirmed that **Z Daily** contains homosildenafil.
FDA May/17 Caverflo.com is voluntarily recalling all lots of **Caverflo Natural Herbal Coffee**, 25 grams to the consumer level. FDA laboratory analysis confirmed the presence of Sildenafil and Tadalafil.
FDA Jun/17 laboratory analysis confirmed that **XXX Zone Platinum & Triple Premium Zen Gold 1300mg** contains sildenafil, tadalafil and dapoxetine.
FDA Jun/17 laboratory analysis confirmed that **Triple X 2000** contains tadalafil and dapoxetine.
FDA Jun/17 laboratory analysis confirmed that **Macho Man 3000, Monster X 1350, Royal Master, & Love Zen 3000** contains tadalafil.
FDA Jun/17 laboratory analysis confirmed that **Own the Knight 1750** contains tadalafil and dapoxetine.
FDA Jun/17 laboratory analysis confirmed that **Xzone Gold, Super Panther 7K & Triple Miracle Zen Plus 1200mg** contains sildenafil and tadalafil.
FDA Jun/17 laboratory analysis confirmed that **Man of Steel 2 & Man of Steel** contains sildenafil.
FDA Jul/17 laboratory analysis confirmed that **Kingdom Honey for Her, Kingdom Honey for Him, & Royal Honey VIP** contains tadalafil.
FDA Jul/17 laboratory analysis confirmed that **Rhino 7 Platinum 5000** contains sildenafil.
FDA Jul/17:**Bestherbs Coffee LLC** is voluntarily recalling all lots of **New of Kopi Jantan Tradisional Natural Herbs Coffee**, 13 grams to the consumer level. FDA laboratory analysis confirmed the presence of desmethyl carbodenafil.
FDA Aug/17: warning consumers not to drink **Longjack Coffee**, in addition to other instant coffee products that have been recalled recently – **Kopi Jantan Tradisional Natural Herbs Coffee, CaverFlo Coffee, and AMPT Coffee**. These products are made in Malaysia, and promoted and sold online for sexual enhancement. These products are labeled to contain instant coffee, non-dairy creamer, and other ingredients. However, FDA laboratory analysis confirmed: **CaverFlo Coffee and AMPT Coffee** contain undeclared sildenafil and tadalafil; **Longjack Coffee and Kopi Jantan Tradisional Natural Herbs Coffee** contain undeclared desmethyl carbodenafil, an analogue of sildenafil; and All of these products contain undeclared milk.
FDA Aug/17: Man of Steel is voluntarily recalling 175 lots of **Man of Steel 1 and Man of Steel 2**, 4000mg at the retail level. The products have been found to contained undeclared Sildenafil.
FDA Sep/17: **Rhino 7, Papa Zen, Fifty Shades, and Grande X** Dietary Supplements by Gadget Island: Recall - Undeclared Drug Ingredients.The products have been found to contain undeclared Active Pharmaceutical Ingredients sildenafil, desmethyl carbodenafil and tadalafil.
FDA Sep/17: Natures Supplement, Inc. is voluntarily recalling 260 bottles of **Vegetable Vigra**, **200 mg capsules** to the consumer level. FDA analysis found this product to be tainted with Sidenafil.
FDA Oct/17 laboratory analysis confirmed that **Tiger 5000** contains sildenafil and tadalafil.
FDA Nov/17 laboratory analysis confirmed that **Hard Times for Men** contains sildenafil.
FDA Dec/17 laboratory analysis confirmed that **Chao Jimengnan** contains sildenafil.
FDA Dec/17: Nutra Labs Inc. is voluntarily recalling lots sold by their firm of the male enhancement supplements **Bull 1800 mg Capsules** with the production date of 05/08/2016, and **Chao Jimengnan 150 mg Tablets** with Lot # 20151018 to the consumer level. FDA analysis found the products to be tainted with sildenafil, 0.026mg/capsule for Bull, and 70.46mg/tablet for Chao Jimengnan respectively.
FDA Dec/17: Marmex Corp is voluntarily recalling all lots of **Blue Pearl All Natural Male Enhancement Supplement**, 500mg to the consumer level. FDA analysis has found the products to contain sildenafil.
FDA Mar/18: laboratory analysis confirmed **that Black Lion Pill contains sildenafil**.
FDA Mar/18: laboratory analysis confirmed that **Red Zone Xtreme 3000 & Rhino 69 Extreme 50000 contains tadalafil**.

FDA Apr/18: Overland Park, KS, Epic Products, LLC is voluntarily recalling all lots of Euphoric capsules, packaged in 1 count blister cards, 3 count bottles, and 12 count bottles to the consumer level. FDA analysis found samples of Euphoric to be tainted with undeclared **sildenafil and tadalafil**,

FDA Apr/18: AMA Wholesale Inc. (Distributor/Re-seller), is voluntarily recalling **Rhino 69 Extreme 50000 capsules** to the consumer level. FDA analysis found the product to be tainted with undeclared **tadalafil.**

FDA May/18: laboratory analysis confirmed that **Best Candy contains nortadalafil**.

FDA May/18: **7K and Poseidon 4500 by Shoreside Enterprises: Voluntary Recall - Due to Presence of Undeclared Sildenafil and Tadalafil.**

FDA July/18: laboratory analysis confirmed that Maximum Powerful contains sildenafil.

FDA Jul/18: laboratory analysis confirmed that Grakcu Capsule, C.U. Plus, Dale Mas contains sildenafil and tadalafil.

FDA Aug/18: laboratory analysis confirmed that XXXPlosion Ultra, Ding Ji Wei Ge, 5K & Panther Power Platinum 11000 contains sildenafil.

FDA Sep/18: laboratory analysis confirmed that Extenze Nutritional Supplement, Extenze Plus, PremierZen Gold 4000 contains sildenafil.

FDA Oct/18: laboratory analysis confirmed that ProSolution, V-Max, USA for Women, Strong Horses & FX75000 contains sildenafil.

FDA Dec/18: laboratory analysis confirmed **that MOB Candy & Willy Go Wild** contains sildenafil and tadalafil,

FDA Dec/18: E-Cialis HelloCig E-Liquid by HelloCig Electronic Technology Co: Warning - Contains the **Undeclared Drugs** Sildenafil and Tadalafil.

FDA Dec/18: E-Rimonabant HelloCig E-Liquid by HelloCig Electronic Technology Co: Warning **- Contains the Undeclared Drug** Sildenafil.

FDA Jan/19: laboratory analysis confirmed that **The Silver Bullet** contains sildenafil and tadalafil.

FDA Jan/19: laboratory analysis confirmed that **Red Stallion** Extra Strong contains tadalafil.

FDA Jan/19: laboratory analysis confirmed that **Natural V=GRA, Yong Gang, Silver Bullet 10x & Black King Kong** contains sildenafil and tadalafil.

FDA Jan/19: laboratory analysis confirmed that **Golden Ant, Instinct Best Sexual Enjoyment & Nectar Del Amor** contains sildenafil.

FDA Jan/19: laboratory analysis confirmed that **Slim Bio Capsules** contain sibutramine, N-desmethylsibutramine, sildenafil, tadalafil, benproperine and diphenhydramine.

FDA Apr/19: **Aphrodisiac Capsules by SD Import: Recall** - Due to Presence of Undeclared Sildenafil.

FDA Apr/19: **BLUEFUSION Capsules by Ata Int.: Recall** - Due to Presence of Undeclared Sildenafil, Tadalafil, Desmethyl Carbodenafil, Dithiodesmethyl Carbodenafil, Scutellarin and Daidzein

FDA May/19: The Beast Capsules by **STIFF BOY: Recall** - Due to Presence of Undeclared Sildenafil

FDA May/19: laboratory analysis confirmed that **Man Fuel Shooter (Tropical Fruit Flavor**) contains tadalafil and desmethyl carbodenafil.

FDA May/19: laboratory analysis confirmed that **Man Fuel Xtreme Edition** contains sildenafil, dithiodesmethyl carbodenafil and desmethyl carbodenafil.

FDA Jun/19: laboratory analysis confirmed that **Peru Maca & Germany Black Gorilla** contains sildenafil.

FDA July/19: laboratory analysis confirmed that **Black Storm, Big Penis, Boss Lion 9000, De Guo Heijin Gang, Herb Viagra, La Pepa Negra, Odimafo Powerful Tablet 200 mg, Plant Vigra, Shengjingpian, & Vigour 800mg** contains sildenafil.

FDA Sep/19: laboratory analysis confirmed that **Mero Macho** contains tadalafil.

FDA Sep/19: laboratory analysis confirmed that **LOBO** contains sildenafil.

FDA Sep/19: laboratory analysis confirmed that **Anaconda Strong Formula, La Pepa Negra, & Lung Leader** contains sildenafil

FDA Sep/19: Fitoterapia is voluntarily recalling **Mero Macho** Artificial Passion Fruit Flavored Vitamin C Liquid Supplement to the consumer level. FDA analysis has found the product to be tainted with tadalafil.

FDA Oct/19**: Green Lumber** (dietary supplements for male sexual enhancement) Capsule Packages by GL Holdings: Recall - Due to Presence of Undeclared Tadalafil

FDA Nov/19: **Up2 by Med Man Distribution**: Recall - Due to Presence of Undeclared Sildenafil.

FDA Nov/19 laboratory analysis confirmed that **Man Erect & SHENGDA & Silver Bullet** (10 Male Enhancement Capsules) contains sildenafil.

FDA Nov/19 reminds consumers not to purchase or use **Power Khan**. An FDA laboratory tested additional samples of Power Khan and found it contained desmethyl thiosildenafil, thioaildenafil, and aildenafil.

FDA Dec/19: laboratory analysis confirmed that **PremierZEN Gold 7000** contains sildenafil and tadalafil.

FDA Dec/19: analysis has found **Bull Platinum 30000, Stallion Platinum 30000, Rhino 7 Platinum 30000, and Panther Platinum 30000** to be tainted with undeclared tadalafil.

FDA Feb/2020: laboratory analysis confirmed that **OrgaZEN Gold 5800** contains sildenafil.

FDA Feb/2020: laboratory analysis confirmed that **Alpha-Male, XXX Platinum WOODIE** contains sildenafil and tadalafil.

FDA Feb/2020: **Up2 and Bow & Arrow** by Med Man: Recall - Due to Presence of Undeclared Sildenafil.

FDA Mar/2020: **Active male** contains tadalafil.

FDA Mar/2020: Natural Remedy Store is voluntarily recalling all lots of **Active Male, 500mg capsules** to the consumer level.

FDA Apr/20: laboratory analysis confirmed that **Black Mamba Premium 18000** contains tadalafil.

FDA Feb/21: Adamssecret.co is voluntarily recalling all lots within expiry of **Adam's Secret Extra** Strength1500 and Adam's Secret Extra Strength 3000 capsules to the consumer level. This recall hasbeen initiated after an FDA laboratory analysis found the product to contain undeclaredsildenafil and/or tadalafil.

FDA Mar/21: laboratory analysis confirmed that 2 Own The Knight Silver 4000, Rhino SE7EN2, Stiff Rox, & Titanium 18K contains sildenafil and tadalafil.

FDA Mar/21: S&B Shopper LLC is recalling all lots of Imperial Extreme 2000 mg capsules because FDA analysis has found this product to contain undeclared sildenafil and tadalafil.

FDA Mar/21: Namoo Enterprise LLC is recalling all lots within expiry of PremierZen Black 5000 capsules because FDA analysis has found the product to contain undeclared sildenafil and tadalafil.

FDA Mar/21: Manassas, VA, Antoto-K is voluntarily recalling all lots of Thumbs Up 7 Red 70K, 10 capsules to consumer level. FDA analysis has found the product to contain undeclared Sildenafil and Tadalafil.

FDA Mar/21: Bit & Bet LLC is voluntarily recalling all lots of Thumbs Up 7 Blue 69K capsules to consumer level. FDA analysis has found the product to contain undeclared sildenafil and tadalafil.

FDA Mar/21: FDA laboratory analysis confirmed that Yin-Yang Essence Men Power, Thumbs Up 7 Red 70K, Thumbs Up 7 Blue 69K, & Furious X 1350, contains sildenafil and tadalafil.

FDA Mar/21: FDA laboratory analysis confirmed that Zing Plus contains sildenafil.

FDA Mar/21: Ummzy is recalling all lots of Thumbs up 7 Red 70K, Shogun-X 15000mg, and Krazy Night capsules because FDA analysis has found the product to contain undeclared tadalafil, sildenafil and vardenafil.

FDA Apr/21: Elmwood Park, NJ, QMART is voluntarily recalling all lots of IMPERIAL Gold 2000, PremierZEN Extreme 3000, BURRO en PRIMAVERA 60000 & IMPERIAL Platinum 2000 to the consumer level. FDA analysis has found the products to be tainted with undeclared sildenafil and/or tadalafil.

FDA Mar/21: S&B Shopper LLC Issues Voluntary Nationwide Recall of **Imperial Extreme 2000mg** Due to Presence of Undeclared Sildenafil and Tadalafil

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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) &/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 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 US 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 & 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.
Health Canada Dec/16 reports: 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.
Health Canada Mar/17: 90° **Jiushidu Capsules, African Viagra, Big Penis Male Sexual Stimulant, Black Mamba 2 Premium, Black 3K Plus Male Sexual Enhancement Capsules, Bl4ck 4K Capsules, Duramaxxx, Power Male Sexual Stimulant, Rhino 5 1500 Capsules, Rhino 7K 9000 Male Performance Booster, Rhino 8 Platinum 8000, Rhino 9 Premium 3500 & Triple Green Capsules** contains undeclared sildenafil.
Health Canada Mar/17: **Megajex Natural Male Sex Enhancer Dietary Supplement** contains undeclared sildenafil & tadalafil.
Health Canada Mar/17: **Chao Jimengnan Super Powerful Man Tablets & Zhen Gongfu** capsules has undeclared sildenafil by the Australian Therapeutic Goods Administration.
Health Canada Mar/17: **GoldReallas Original & GoldReallas XXX** has undeclared sildenafil & thiosildenafil by the FDA.
Health Canada Mar/17: **Impeous Man capsules** has undeclared sildenafil & phenolphthalein by the Australian Therapeutic Goods Administration.
Health Canada Mar/17: **Old Chinese & Shenjingpian** has undeclared sildenafil by the FDA.
Health Canada Mar/17 is advising Canadians that it has seized multiple unauthorized health products from three retailers in Ontario (see table below). The products are promoted for sexual enhancement and were found to contain, or are labelled to contain, prescription drugs that may pose serious risks to the health of Canadians. Hespeler Road Adult SuperStore (261 Hespeler Road, Cambridge ON): **LipsTenZen, Super Panther 7K & Thunder Bull 7K contains Yohimbe. One More Knight contains tadalafil and dapoxetine. MV7 Days 2000** contains sildenafil and tadalafil. Naughty Shop (330 Wellington Rd. S, London ON): **LipsTenZen, Super Panther 7K & Triple Green** contains Yohimbe.
VXI Multimedia (800 Petrolia Road, Unit 18, Toronto, ON): **Opti-Sildenafil** 100 mg contains sildenafil, **Opti-Tadalafil** 20 mg contains tadalafil.
Health Canada Apr/17 is advising Canadians that the unauthorized health product "**Rhino Blitz Gold**" may pose serious health risks, after testing confirmed it contains an undeclared prescription drug (sildenafil).

Health Canada Apr/17 laboratory tests have confirmed that two additional unauthorized products seized from **24 Hour Adult Mart in Toronto** contain undeclared tadalafil.
Health Canada May/17: **Africa Black Ant capsules & Australia Kangaroo Essence** by Australia Therapeutic Goods Administration has undeclared sildenafil.
Health Canada May/17: **Arouse-Plus & Bazook Bullet** by FDA has undeclared tadalafil.
Health Canada May/17 is advising Canadians that multiple unauthorized health products seized from **two retailers in Scarborough, ON**, may pose serious risks to health. Products seized include "poppers" and products promoted for sexual enhancement. Adult Store 2365 Eglinton Ave E Scarborough ON had Rochfort 10mL-Isobutyl nitrite; Finegra-100-Sildenafil; Super Panther 7K-Yohimbe; Premium X Pulse 2000-Yohimbe; Premium Pro Power 3500-Yohimbe bark extract; Hard Rock 3800-Yohimbe bark extract; XXL Ant 3000-Yohimbe bark extract; Black Mamba 2 Premium-Yohimbe; Mamba is Hero-Yohimbe, sildenafil, desmethyl carbodenafil and dapoxetine; Master Zone 1500- Sildenafil and tadalafil. Homerama Adult Video 2524 Eglinton Ave E Scarborough had ONWet XXX-Yohimbe; 7K-Yohimbe; Super Panther 7K-Yohimbe; Passion Classic- Yohimbe; Titanium 4000-Sildenafil and tadalafil. Adult Store 2365 Eglinton Ave E Scarborough ON had Zhen Gongfu-previous testing of product with similar packaging, identified as containing undeclared sildenafil; Stiff Rock- previous testing of product with similar packaging, identified as containing undeclared sildenafil; One For Her- Previous testing of product with similar packaging, identified as containing undeclared tadalafil; Rush 10mL, Super Rush 10mL & Blue Boy 10mL-previously seized products with similar packaging were labelled to contain alkyl nitrites. Homerama Adult Video 2524 Eglinton Ave E Scarborough ON had Rush 10mL, Super Rush 10ml, Jungle Juice Gold Label 10mL, Jungle Juice Gold Label 30mL, Jungle Juice Platinum 10mL, & Jungle Juice Platinum 30mL previously seized products with similar packaging were labelled to contain alkyl nitrites.
Health Canada June/17: **VENERGY Capsule** 100mg has undeclared sildenafil by the Hong Kong Department of Health.
Health Canada June/17: **Nangen Zengzhangsu** undeclared sildenafil by Australia Therapeutic Goods Administration.
Health Canada June/17: **Slim-Vie Slimming Capsules** has undeclared sibutramine, sildenafil, and phenolphthalein by Australia Therapeutic Goods Administration.
Health Canada Jul/17: **Big N Hard** has undeclared tadalafil by the United States Food and Drug Administration.
Health Canada Jul/17: **Black Gorilla, Maxman IV, Maxman Premium, Maxman V, MMC Maxman XI, New Advanced Technological, V9 Male Sexual Stimulant, Real Skill Male Sexual Stimulant, & Rize N Shine** has undeclared sildenafil by the Australia Therapeutic Goods Administration.
Health Canada Jul/17: **Cummor & Monkey Business** has undeclared N-desmethyl tadalafil by the United States Food and Drug Administration.
Health Canada Jul/17: **Dragon Max, Oh Baby!, & XXXL Penis Enlarging Ointment** has undeclared tadalafil by the Australia Therapeutic Goods Administration.
Health Canada Jul/17: **Tornado** has undeclared nortadalafil by the United States Food and Drug Administration.
Health Canada Jul/17: **Xrect** has undeclared tadalafil and descarbonsildenafil by the United States Food and Drug Administration.
Health Canada Jul/17: **Z Daily** has undeclared homosildenafil by the United States Food and Drug Administration.
Health Canada Mar/18: is advising Canadians that two versions of the sexual enhancement product "**Leopard Miracle of Honey**" may pose serious health risks. Both versions are labelled as being approved by Health Canada, with NPN 80073650. Health Canada's testing found that both versions of the product contain the undeclared prescription drug sildenafil.
Health Canada Nov/19: is advising Canadians that **Passion X & Passion Fem** contains undeclared sildenafil.
Health Canada Feb 2020: laboratory testing found that **Performance Plus capsules & Never Rest** contains a prescription drug sildenafil.
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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.
MHRA Sep/17 investigators raided **Antley's** property and seized more than 13,900 doses of unlicensed erectile dysfunction medicines worth more than £40,000. Antley pleaded guilty to the charges and was sentenced to 20 weeks imprisonment (concurrent to all counts). Gurinder Bharaj, of Southall, West London, was sentenced on Friday at Isleworth Crown Court on eight counts of possession and supply of significant quantities of unauthorised and unlicensed medication. Investigators from the Medicines and Healthcare products Regulatory Agency (MHRA) raided a property belonging to Mr Bharaj in Ealing where more than 100,000 individual doses of unlicensed erectile dysfunction medicines worth more than £30,000 were uncovered and seized. A smaller quantity of prescription medication was also seized.
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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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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
Five things to know about ...: Superficial dyspareunia: http://www.cmaj.ca/content/189/24/E836.full
Treatment of Vulvovaginal Atrophy – JAMA Sept 2019: https://jamanetwork.com/journals/jama/fullarticle/2752418

INTRINSA testosterone patch, discontinued; previously available in Europe.

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Additional references: **Sexual Dysfunction**: Overview & Drug Considerations (www.RxFiles.ca)

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FDA Dec/13 is warning that **methylphenidate products**, one type of stimulant drug used to treat attention deficit hyperactivity disorder (ADHD), may in rare instances cause prolonged and sometimes painful erections known as **priapism**.
FDA Apr/19 has determined that changes must be made to **Addyi's** labeling to clarify that there is still a concern about consuming alcohol close in time to taking Addyi but that it does not have to be avoided completely.
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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:**[84] tertiary amine with ACh & calcium channel antagonist activity; see chart above.

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]

Vibegron – new β3-adrenergic receptor agonist for OAB {not yet available in }

- Vibegron 75mg/d vs. Tolteradine 4mg/d vs. placebo[EMPOWUR]

Treatment group (85% ♀, 43%≥65y)	Micturations/day at baseline (median)	Micturation frequency at 12 weeks	Urgency episodes/day (median)	Urgency episodes/day at 12 weeks	Volume voided (mL/micturition) (median)	Volume voided at 12 weeks (mL/micturition)	Safety, Tolerability
Vibegron 75mg/d (n=526)	10.4	-1.8 episodes/day	7.8	-2.7	150.0	+23.5	1.7% d/c. A/E: UTI$_{5\%}$, HA$_{4\%}$, nasopharyngitis$_{2.8\%}$, diarrhea$_{2.2\%}$, nausea$_{2.2\%}$. HTN$_{1.7\%}$, no tachycardia. Serious: pneumonia, noncardiac chest pain (2 patients)
Tolteradine 4mg/d (n=417)	10.6	-1.6 episodes/day	8.0	-2.5	143.3	+15.5	3.3% d/c. A/E: UTI$_{5.8\%}$, dry mouth$_{6.5\%}$, HTN$_{2.6\%}$, HA$_{2.6\%}$, nasopharyngitis$_{2.6\%}$, diarrhea$_{2.1\%}$
Placebo (n=520)	10.4	-1.3 episodes/day	8.0	-2.0	141.7	+2.2	1.1% d/c. A/E: UTI$_{6.1\%}$, HA$_{2.4\%}$, nasopharyngitis$_{1.7\%}$, diarrhea$_{1.1\%}$, upper respiratory-tract infecton$_{0.7\%}$, nausea$_{1.1\%}$, HTN$_{1.7\%}$, dry mouth$_{0.9\%}$

d/c=discontinued HA=headache HTN=hypertension UTI=urinary tract infection
Vibegron showed statistically significant improvement for overactive bladder compared to placebo starting from 2 weeks until 12 weeks.

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

Low risk of high-grade prostate cancer with 5-ARIs (finsteride 5mg {1.8% vs. 1.1% placebo in 7 yrs, no difference in mortality after 18 years follow-up}[PCPT] or dutasteride 0.5mg/d {1% vs. 0.5% placebo in 4 yrs}[REDUCE])[FDA]

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Vaccines: Adults, Online Extras

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Complete ABBREVIATIONS: ‡=adjuvant containing vaccine ❄=refrigerate **AAP**=American Academy of Pediatrics **ACIP**=Advisory Committee on Immunization Practices **AE(s)**=adverse effect(s) **anti-HBs**=anti-hepatitis B surface antigen **BCG**=bacille Calmette-Guerin **CDN**=Canadian **CI**=contraindication **CKD**=chronic kidney disease **COVID**=coronavirus disease 2019 **CVD**=cardiovascular disease **d**=day(s) **DIs**=drug interactions **DMARDs**=disease-modifying antirheumatic drugs **DTaP**=diphtheria, tetanus, acellular pertussis (pediatric formulation) **dx**=disease **ELISA**=enzyme-linked immunosorbent assay **EtOH**=alcohol **FDA**=approved Food & Drug Admin **HA**=headache **HAV**=hepatitis A virus **HBsAg**= Hep B "surface" antigen **HBV**=hepatitis B virus **HCV**=hepatitis C virus **HD**=hemodialysis **Hib**=*Haemophilus influenzae* type b **HIV**=human immunodeficiency virus **HPV**=human papillomavirus **hr(s)**=hour(s) **HSCT**=hematopoietic stem cell transplantation **IBD**=inflammatory bowel disease **Ig**=immunoglobulin **IGRA**=interferon gamma release assay **IM**=intramuscular **IPV**=inactivated polio vaccine **IU**=international units **kg**=kilograms **L**=litres **LTC**=long term care **mcg**=microgram **mg**=milligrams **min(s)**=minute(s) **mL**=millilitres **MMR**=measles, mumps, rubella **mo(s)**=month(s) **MS**=multiple sclerosis **MSM**=men who have sex with men **NACI**=National Advisory Committee on Immunization **NNH**=number needed to harm **NNT**=number needed to treat **N/V/D**=nausea/vomiting/diarrhea **PCV**=Pneumococcal Conjugate Vaccine **PD**=peritoneal dialysis **po**=oral **PPSV**=Pneumococcal polysaccharide vaccine **RA**=rheumatoid arthritis **SIM**=Saskatchewan Immunization Manual **SK**=Saskatchewan **SLE**=systemic lupus erythematosus **SOGC**=Society of Obs & Gyne of Canada **Td**=tetanus, diphtheria **Tdap**=tetanus, diphtheria, acellular pertussis (adolescence/adult formulation) **TST**=tuberculin skin test **URTI**=upper respiratory tract infection **VZV**=varicella-zoster virus **wk(s)**=weeks **yr(s)**=year(s)

Potential Allergens: some adult vaccines, for a complete list see: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-1-key-immunization-information/page-15-contents-immunizing-agents-available-use-canada.html

Neomycin:
- **ADACEL-POLIO**, **BOOSTRIX-POLIO**, **TD POLIO ADSORBED**, **IMOVAX POLIO**
- **AFLURIA TETRA**, **AGRIFLU**, **FLUAD**
- **AVAXIM**, **HAVRIX**, **VAQTA**, **TWINRIX**
- **M-M-R-II**
- **VARILRIX**, **VARIVAX III**
- **ZOSTAVAX**

Polymyxin:
- **ADACEL-POLIO**, **BOOSTRIX-POLIO**, **IMOVAX POLIO**, **TD POLIO ADSORBED**
- **AFLURIA TETRA**, **FLUAD**

Streptomycin:
- **ADACEL-POLIO**, **IMOVAX POLIO**

Thimersol:
- **AFLURIA TETRA**, **AGRIFLU**, **FLULAVAL TETRA**, **FLUVIRAL**, **FLUZONE QUADRIVALENT**
- **ENGERIX-B**

Latex containing (e.g. in plunger of syringe)**:**
- **RECOMBIVAX HB**, **VAQTA**
- **CERVARIX**
- **BEXSERO**, **MENJUGATE**

Gelatin:
- **FLUMIST QUADRIVALENT**
- **M-M-R-II**
- **VARIVAX III**
- **ZOSTAVAX**

Gentamicin:
- **FLUMIST QUADRIVALENT**, **INFLUVAC**

Other Vaccines:
- **YF-VAX**: Yellow Fever $140;
- **IMOVAX-Rabies**, **RabAvert**: Rabies $700/3-5 doses; Rabies Immune Globulin (acute exposure, give within 24hrs or up to 7 days after 1st dose of rabies vaccine);
- **TYPHIM-Vi**, **TYPHERIX**:Typhoid IM $36; **VIVOTIF**: Typhoid oral; **VIVAXIM**: HAV & Typhoid HAV-Typh-I;
- **JE-VAX**/ixiaro: Japanese Encephalitis $615/series;
- **DUKORAL**: oral for select cholera strains $130-195/series;
- **DENGVAXIA**: FDA'19 age 9-16yr if dengue lab confirmed dx, 4 serotypes, live, 3 doses.

Passive Agents: Antitoxin: botulism & diphtheria; Immuglobulin: human, HBV, rabies, RSV, tetanus & varicella; Antivenom: snake & spider

Helpful Links

- CAN: National Advisory Committee on Immunization (**NACI**)
  - Canadian Immunization Guide (**CIG**)
  - Immunize Canada & CANImmunize App
  - "Vaccines Work" patient infographic
- US: Centers for Disease Control and Prevention
  - Advisory Committee on Immunization Practices (**ACIP**)
- SK: Saskatchewan Immunization Services
  - Saskatchewan Immunization Manual (**SIM**)
- Reporting AEs: Adverse Event Following Immunization (**AEFI**)
- RxFiles Q&A Vaccines: Pneumococcal, Influenza, Shingles
- Geri-RxFiles: Vaccines for Older Adults

ADACEL	79
BEXSERO	79
BOOSTRIX	79
CERVARIX	79
Diphtheria	79
ENERGIX-B	79
FLUAD	79
FLUMIST	79
GARDASIL	79
Haemophilus	79
Hepatitis	79
HPV vaccine	79
Immunization	79
Influenza	79
Inoculation	79
Measles	79
Meningococcal	79
MMR	**79**
Mumps	79
Pertussis	79
Pneumococcal	**79**
PNEUMOVAX	79
Polio	79
PREVNAR	79
Rabies	79
Rubella	79
Shingles	79
SHINGRIX	79
Tetanus	79
Vaccine	**79**
Varicella	79
ZOSTAVAX	79
Zoster	79
ACT-HIB	80
ADACEL	80
AVAXIM	80
BEXSERO	80
BOOSTRIX	80
CERVARIX	80
ENERGIX-B	80
FENDRIX	80
GARDASIL	80
HAVRIX	80
Heplisav-B	80
IMOVAX	80
MENACTRA	80

MENJUGATE	80
MENVEO	80
MMR	**80**
NEISVAC-C	80
NIMENRIX	80
Pneumococcal	**80**
PNEUMOVAX	80
Polio	80
PREVNAR	80
RECOMBIVAX	80
Shingles	80
Td Adsorbed	80
Tetanus	80
Travel	80
TRUMENBA	80
TWINRIX	80
Vaccine	**80**
VAQTA	80
VARILRIX	80
VARIVAX	80
ZOSTAVAX	80
Zoster	80
SHINGRIX	80
Inoculation	80
Measles	80
Meningococcal	80
Rubella	80
Mumps	80
Pertussis	80
HPV vaccine	80
MENQUADFI	80

References for Vaccines Comparison Chart:

General

RxTx – Vaccine Product Monographs

Epocrates - Vaccine Product Monographs

DPDB

Pharmaclick

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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 are contraindicated during pregnancy, as there is a, largely theoretical, risk to the fetus. (II-3) 4. Women who have inadvertently received immunization with live or live-attenuated vaccines during pregnancy should not be counselled to terminate the pregnancy because of a teratogenic risk. (II-2) 5. Non-pregnant women immunized with a live or live-attenuated vaccine should be counselled to delay pregnancy for at least four weeks. (III) 6. Inactivated viral vaccines, bacterial vaccines, and toxoids are considered safe in pregnancy. (II-1) 7. Women who are breastfeeding can still be immunized (passive-active immunization, live or killed vaccines). (II-1) 8. Pregnant women should be offered the influenza vaccine when pregnant during the influenza season. (II-1).
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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 May/10 is advising Canadians and Canadian healthcare practitioners that we are currently reviewing new information regarding the presence of porcine circovirus (PCV-1 and PCV-2) DNA in rotavirus vaccines. Porcine circovirus is a single stranded DNA virus, and is considered a contaminant in these vaccines.
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.
Health Canada Oct/16 An increased risk of hemolysis or low hemoglobin has been observed when patients already being treated with SOLIRIS (**eculizumab**) were vaccinated against serogroup B **meningococcal** infection with Bexsero.
Health Canada May/18: Several **GlaxoSmithKline Inc. vaccines: Potential Risk of Underdosing**- There have been reports of leakage from ceramic coated tip syringes used for several GlaxoSmithKline Inc. vaccines during vaccine preparation or administration. Although the leakage does not pose a concern for the vaccine sterility, there is a potential risk of underdosing associated with administration of a vaccine from a leaking syringe that may leave patients inadequately protected from disease after vaccination.
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continue to receive all five vaccine shots, with the fifth on Day 28. Vaccine shots may be delivered to the outer aspect of the thigh in younger children and to the deltoid in older children and adults. The gluteal region should never be used.The authors note that their recommendations will differ from vaccine label instructions into the foreseeable future.MMWR Recommendations and Reports: http://cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm
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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 ~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

Antifungal	**81**
Athlete's Foot	**81**
Candidiasis	81
CANESORAL	81
CANESTEN	81
Ciclopirox	81
Clotrimazole	81
Dermatophyte	81
DESENEX	81
Diaper Rash	81
Efinaconazole	81
EMTRIX	81
Fungal	**81**
FUNGICURE	81
JUBLIA	81
Ketoconazole	81
LAMISIL	81
LOPROX	81
MICATIN	81
Miconazole	81
MONICURE	81
MONISTAT	81
MYCOSTATIN	81
NIZORAL	81
Nystatin	81
Onychomycosis	81
PENLAC	81
Pityriasis Versicolor	81
Seborrheic Dermatitis	81
STIEPROX	81

TERAZOL	81
Terbinafine	81
TINACTIN	**81**
Tinea Versicolor	**81**
Tolnaftate	**81**
Vulvovaginal Candidiasis	**81**
Antifungal	**82**
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FDA Oct/12: The FDA and the CDC are recommending that clinicians stop using *all* products from the New England Compounding Center, which is a suspected source in an outbreak of fungal meningitis. To date, 105 people in nine states have been infected following injections of the company's epidural steroid, and eight people have died.
FDA Jan/16 is cautioning that differences in dosing regimens between the **two oral formulations of the antifungal Noxafil (posaconazole) have resulted in dosing errors**. To help prevent additional medication errors, the drug labels were revised to indicate that the two oral formulations cannot be directly substituted for each other but require a change in dose. Direct mg for mg substitution of the two formulations can result in drug levels that are lower or higher than needed to effectively treat certain fungal infections.
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Oral Antibiotics: Online Extras

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Rifampin: Monotherapy for treatment for latent TB and prophylaxis for meningococcal disease. Risk of developing resistance if used as monotherapy. Many significant number of drug interactions.

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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Note: For kids who dislike the taste of antibiotics – may consider a chocolate syrup chaser. See: https://www.sciencedirect.com/science/article/pii/S0011393X00800399

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Acute Otitis Media: Pediatric Management Considerations

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APPENDIX C

A. INCISION AND DRAINAGE (I&D) PROCEDURE

Adapted from US Federal Bureau of Prisons MRSA CPG April 2011

Abscesses are localized infections of tissue marked by a collection of pus surrounded by inflamed tissue. Abscesses may be found in any area of the body; those requiring more urgent attention are found on the extremities, face, buttocks, breast, perianal area, axilla, groin. Abscesses begin when the normal skin barrier is breached, and microorganisms colonize the underlying tissues. Causative organisms commonly include *Streptococcus sp.*, *Staphylococcus sp.*, enteric bacteria (perianal abscesses), or a combination of anaerobic and gram-negative organisms.
Abscesses resolve by drainage. Smaller abscesses may resolve with conservative measures (warm soaks) to promote spontaneous drainage. Larger abscesses will require incision to drain them (I & D) as the increased inflammation, pus collection, and walling-off of the abscess cavity diminish the effectiveness of antibiotic treatment. Healing following I & D should progress from the inside of the abscess outward to the incision site. For larger abscesses this may require a gauze packing to promote healing from the inside outward (See Part B below: Role of Packing for an Abscess)

NOTE:

- Extremely large abscesses that require extensive incision, debridement, or irrigation are best done in operating room.
- Deep abscesses in very sensitive areas (labial, supralevator, ischiorectal, perirectal) pften require a general anesthetic to obtain proper exposure.
- Abscess in the hands or feet are best drained by a surgeon. Deep palmar abscesses are a surgical emergency.
- Abscesses in the triangle formed by the bridge of the nose and the corners of the mouth should generally be treated with warm compresses and aggressive antibiotic therapy.
- Abscesses located near major vessels must be differentiated from aneurysms before I & D is performed to avoid fatal hemorrhage. The distinction is made through aspiration with a large bore needle, or with ultrasound guidance.

PROCEDURE

- **The information below applies to an abscess within the skin and subcutaneous tissue that is palpable.**
- **Obtain informed consent.**
- **Use Routine/Standard Infection Control Precautions, and sterile technique.**

1. Infiltrate local anesthetic, allowing 2–3 minutes for anesthetic to take effect. Remember that tissue around an abscess is acidotic and local anesthetic is less effective. Consider doing a field block.
2. Incise over abscess with the scalpel blade, cutting through the skin into the abscess cavity. Follow skin fold lines whenever possible while making the incision. The incision should be sufficiently wide to allow the abscess to drain and to prevent premature closure of the incision.
   For smaller abscesses requiring incisions, a stab or cruciate incision should be adequate. Some refer to this as a puncture or stab technique since the operator inserts the tip of the scalpel directly into the center of the abscessed tissue without making a linear incision. If a culture is being obtained, use the culture swab to take culture of abscess contents, swabbing inside the abscess cavity—not from the superficial skin over the abscess.
3. Use a hemostat or sterile cotton-tipped applicator to gently explore the abscess cavity to break up any loculations within the abscess.
4. Loosely pack the abscess cavity with the packing (if indicated).
5. Place gauze dressing over the wound, and tape in place. Topical antibiotic is not required.
6. Schedule patient to return for review within 24–48 hours post-procedure. Depending upon the location and size of the abscess, arrange for the packing material to be changed daily.
7. Pain from the site may require acetaminophen or nonsteroidal anti-inflammatory drugs; narcotics are rarely needed.

Following I & D of any abscess:

- Routine use of oral antibiotics after uncomplicated I & D is NOT recommended. Antibiotics have a role for patients with complicated abscesses (such as those with systemic symptoms), immunocompromised patients, and for abscesses with significant surrounding cellulitis or in areas difficult to drain, such as the hand.
- The site should be observed for signs of recollection of pus or cellulitis.

- Complications of an inadequately treated abscess include bacteremia and septicemia.
- In persons who are immunocompromised, particularly people with diabetes or peripheral arterial disease, an abscess on an extremity can be complicated by severe cellulitis or gangrene, with potential loss of the affected extremity.

Post-Procedure Patient Education.

- Patients should be instructed to watch for the following symptoms:
  - Recollection of pus in the abscess
  - Fever and chills
  - Increased pain and redness
  - Red steaks near the abscess
  - Increased swelling

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B. ROLE OF PACKING FOR AN ABSCESS

Packing of wounds – there is no scientific evidence to support packing of wounds after I&D of a simple cutaneous abscess.
Studies (RCT) looking at outcomes from packing of simple abscesses are limited in number and of small size. O'Malley *et al* demonstrated no difference in outcomes in patients who had I&D, standard wound irrigation and packing or no packing, however the packing group reported more pain and use of analgesics. There were no significant differences between groups in need for second intervention at 48 hours.
Packing of cutaneous abscesses is not usually done in developing countries with no significant problems. Clinical follow-up at 48 hours after I & D of simple cutaneous abscess is important whether wound is packed or not.

Reference:
O'Malley GF etal. Routine Packing of Simple Cutaneous Abscesses Is Painful and Probably Unnecessary Academic Emergency Medicine 2009; 16:470–473

C. CULTURING CELLULITIS

The diagnosis of cellulitis is based on the clinical features. Cellulitis associated with furuncles, carbuncles, or abscesses is usually caused by *S.aureus*. In contrast, cellulitis that is diffuse or unassociated with a defined portal is most commonly caused by streptococcal species.

- For outpatients with **non-purulent cellulitis**, **cultures** will usually grow normal skin flora and are therefore **not routinely recommended**.
  - Empirical therapy for infection due to beta-hemolytic streptococci is recommended.
  - Empirical coverage for MRSA may be considered in those with systemic signs and symptoms and is recommended in patients who do not respond to initial therapy.

- For outpatients with **purulent cellulitis** in the absence of a drainable abscess, **swab purulent drainage or exudate and send for culture.**
  - Empirical therapy for infection due to beta-hemolytic streptococci is not likely necessary.
  - Empirical therapy for MRSA may be considered pending culture results.

Other microbiological investigations including aspiration and punch biopsies are not routinely recommended because results are rarely positive. Blood cultures are recommended when there are signs and symptoms of systemic illness.

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Cephalosporin	96
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Cephalosporin	98
Clindamycin	98
Cloxacillin	98
COTRIMOXAZOLE	98
DALACIN	98
DOXYCIN	98
Doxycycline	98
ERYC	98
Erythromycin	98
KEFLEX	98
MRSA	98
MSSA	98
Non-Purulent	98
OZANEX	98
Purulent	98
SEPTRA	98
Skin Infection	**98**
Antibiotic	99
BACTRIM	99
Cellulitis	99
Cephalosporin	99
Clindamycin	99
COTRIMOXAZOLE	99
DALACIN	99
MRSA	99
Non-Purulent	99
Purulent	99
SEPTRA	99
Skin Infection	**99**

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Desensitization template[17]

The goal of desensitization is to gradually increase the rate of antibiotic such that immune response is altered, and temporary tolerance is conferred. A 12-step protocol is commonly used, starting with a very low concentration of antibiotic (e.g. 1/50,000) and gradually increasing to target dose every 15 minutes.

Obtain patient consent prior to protocol start. Throughout the protocol, take vitals every 15 minutes (q30 minutes during last step). At conclusion of protocol, observe patient carefully for 30 minutes - then can give full therapeutic dose at usual schedule.

If patient has a severe reaction during protocol (e.g. hypotension, throat swelling, bronchospasm), stop the infusion and treat with **epinephrine** 0.3mg IM, **diphenhydramine** 50mg IV and **methylprednisolone** 50mg IV, 2 puffs of inhaled **salbutamol** 100mcg (if bronchospasm), and IV fluids.

Step 1	1/50,000th	of usual dose given over 15 minutes
Step 2	1/20,000th	of usual dose given over 15 minutes
Step 3	1/10,000th	of usual dose given over 15 minutes
Step 4	1/5,000th	of usual dose given over 15 minutes
Step 5	1/2,000th	of usual dose given over 15 minutes
Step 6	1/1,000th	of usual dose given over 15 minutes
Step 7	1/500th	of usual dose given over 15 minutes
Step 8	1/250th	of usual dose given over 15 minutes
Step 9	1/100th	of usual dose given over 15 minutes
Step 10	1/50th	of usual dose given over 15 minutes
Step 11	1/25th	of usual dose given over 15 minutes
Step 12	~90%	of usual dose given slowly over ~3 hours

Sample Desensitization Protocol for Ceftriaxone (adapted with permission from the Saskatoon Health Region)

1. Prepare Solutions **One**, **Two**, and **Three**

			Total mg per bag	**Amount of bag infused**
Solution **One**	250 mL of	0.08 mg/mL	20mg	9.25 mL*
Solution **Two**	250 mL of	0.8 mg/mL	200mg	18.75 mL*
Solution **Three**	250 mL of	8 mg/mL	2000mg	248 mL

* Discard unused portions of the minibag

2. Infuse Solutions as follows:

Dose Number	Solution Number	Infusion Rate (mL/hr)	Time	Volume Infused	Dose Administered	Cumulative Dose
Step 1	Solution **One**	2	15 minutes	0.5 mL	0.04 mg	0.04 mg
Step 2		5	15 minutes	1.25 mL	0.1 mg	0.14 mg
Step 3		10	15 minutes	2.5 mL	0.2 mg	0.34 mg
Step 4		20	15 minutes	5 mL	0.4 mg	0.74 mg
Step 5	Solution **Two**	5	15 minutes	1.25 mL	1 mg	1.74 mg
Step 6		10	15 minutes	2.5 mL	2 mg	3.74 mg
Step 7		20	15 minutes	5 mL	4 mg	7.74 mg
Step 8		40	15 minutes	10 mL	8 mg	15.74 mg
Step 9	Solution **Three**	10	15 minutes	2.5 mL	20 mg	35.74 mg
Step 10		20	15 minutes	5 mL	40 mg	75.74 mg
Step 11		40	15 minutes	10 mL	80 mg	155.74 mg
Step 12		80	175 minutes	230.5 mL	1844 mg	2000 mg

Total time = 338 minutes = 5 hours 38 minutes

Allergy	100
Amoxicillin / Clavulanate	100
Amoxicillin	100
AMOXIL	100
Ampicillin	100
ANCEF	100
Antibiotic	100
Beta-Lactam	**100**
Cefadroxil	100
Cefazolin	100
Cefepime	100
Cefixime	100
Cefotaxime	100
Cefprozil	100
Ceftazidime	100
CEFTIN	100
Ceftriaxone	100
Cefuroxime	100
CEFZIL	100
Cephalexin	100
Cephalosporin	100
CLAFORAN	100
CLAVULIN	100
Cloxacillin	100
DURICEF	100
FORTAZ	100
KEFLEX	100
Penicillin	100
Penicillin Allergy	**100**
PEN-VK	100
ROCEPHIN	100
Serum Sickness	100
SUPRAX	100

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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. **tx-child** (not newborn): Bacitracin-polymyxin B or Erythromycin oint 0.5% QID.
- **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 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.
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.
FDA Jan/18: AuroMedics Pharma LLC is voluntarily **recalling** one lot of **Levofloxacin** in 5% Dextrose Injection 250mg/50mL in a Single-Use flexible container NDC 55150-243-46, Lot CLF160003, Expiry date May 2018, to the hospital level. The product has been found to contain visible particulate matter tentatively identified as mold. This problem was discovered as a result of a product complaint in which the contents of one flexible bag was found to contain white particulate matter.
FDA Mar/18 : FDA is advising caution before prescribing the antibiotic **clarithromycin** (Biaxin) to patients **with heart disease** because of a potential increased risk of heart problems or death that can occur years later. FDAs recommendation is based on a review of the results of a 10-year follow-up study of patients with coronary heart disease from a large clinical trial that first observed this safety issue.
FDA Jul/18: FDA is strengthening the current warnings in the prescribing information that **fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects**. The new label changes will add that low blood sugar levels, also called hypoglycemia, can lead to coma and the new label will also make the mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class. The mental health side effects to be added to or updated across all the fluoroquinolones are: disturbances in attention, disorientation, agitation, nervousness, memory impairment, serious disturbances in mental abilities called delirium.
FDA Aug/18: **Zithromax, Zmax (azithromycin): FDA Warning** - Increased **Risk of Cancer Relapse** With Long-Term Use After Donor Stem Cell Transplant.
FDA Dec/18: review found that **fluoroquinolone antibiotics can increase the occurrence of rare but serious events of ruptures or tears in the main artery of the body, called the aorta**.
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Health Canada Nov/11 **Fluoroquinolone** antibiotics: patients with **myasthenia gravis** may risk increased muscle weakness.
Health Canada May/13: Zithromax/Zmax SR (**azithromycin**) - Risk of Potentially Fatal Irregular (**QT**) Heart Beats - Pfizer Canada Inc.
Health Canada. Notice – antimicrobials product labelling. November 16, 2015. www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/announce-annonce/notice-amr-avis-ram-eng.php (accessed November 27, 2015). (Health Canada is mandating the inclusion of precautionary statements in **antimicrobial product labelling to encourage prudent prescribing and use of antimicrobial drugs**.)
Health Canada Dec/15: **Biseptol 480** contains sulfamethoxazole & trimethoprim.
Health Canada Dec/15: **Oxycort** contains oxytetracycline & hydrocortisone.
Health Canada's Jan/17 recent safety review of oral and injectable **fluoroquinolones**, a class of antibiotics, found that in rare cases some known side effects may be persistent or disabling. This includes muscular issues such as tendonitis and Achilles tendon rupture, nerve damage such as peripheral neuropathy, and central nervous system issues such as anxiety, dizziness and confusion.
Health Canada Aug/18 is warning Canadians of the potential **risk of cancer relapse in patients with cancer of the blood and lymph nodes who have undergone stem cell transplant and are taking long-term azithromycin** (Zithromax). **HealthMap** http://www.healthmap.org/en/
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Indications & Regimens (continued): Genotypes 1-3, regimens used less often.

	GT1a				GT1b				GT2				GT3			
	noncirrhotic		comp. cirrhosis		noncirrhotic		comp. cirrhosis		noncirrhotic		comp. cirrhosis		noncirrhotic		comp. cirrhosis	
	Naïve	Experienced	Naïve	Exp.	Naïve	Exp.	Naïve	Exp.	Naïve	Exp.	Naïve	Exp.	Naïve	Exp.	Naïve	Exp.
SOF + DCV	12 wks $93-97K	12 wks $93K	-	-	12 wks $93-97K	12 wks $93K	-	-	12 wks $93K	-	16-24 wks $124-186K	-	12 wks $93K	12 wks $93K	24 wks + RBV $195K	24 wks + RBV $195K
DCV + ASV	24 wks + PEGI + RBV, $95K				24 wks, $85K				-				-			
SOF + SIM	12 wks[d], $91K		24 wks[d], $182K		12 wks[d], $91K		24 wks[d], $182K		-				-			
SOF + RBV	-				-				12 wks[h], $58K				24 wks[h], $117K			
SOF + PEGI + RBV	12 wks, $59K				12 wks, $59K				12 wks, $59K				12 wks, $59K			

d. Previous null responders should avoid SIM. Patients previously failing therapy with a protease inhibitor should avoid SIM (and other protease inhibitors eg. BOC, TVR).
h. Avoid if decompensated cirrhosis (i.e. Child-Pugh Class B or C).

Indications & Regimens (continued): Genotypes 4-6. Nov 2019

	GT4				GT5				GT6			
	noncirrhotic		comp. cirrhosis		noncirrhotic		comp. cirrhosis		noncirrhotic		comp. cirrhosis	
	Naïve	Experienced	Naïve	Exp.	Naïve	Exp.	Naïve	Exp.	Naïve	Exp.	Naïve	Exp.
HARVONI SOF/LDV	12 wks, $67K			12 wks + RBV $71K	12 wks, $67K				12 wks, $67K			
TECHNIVIE ✗ ⊗ PTV/RTV/OBV	12 wks + RBV, $56K				-				-			
ZEPATIER ✗ ⊗ EBR/GZR	12 wks $56K	16 wks + RBV $85K	12 wks $56K	16 wks + RBV $85K	-				-			
EPCLUSA ✗ ⊗ SOF/VEL	12 wks, $60K				12 wks, $60K				12 wks, $60K			
	Solfosbuvir + velpatasvir is indicated for all HCV genotypes (1 to 6). Add RBV if decompensated cirrhosis (i.e. Child-Pugh Class B or C).											
MAVIRET GLE/PIB	8 wks $40K	8 wks $40K	12 wks $60K	12 wks $60K	8 wks $40K	8 wks $40K	12 wks $60K	12 wks $60K	8 wks $40K	8 wks $40K	12 wks $60K	12 wks $60K
VOSEVI SOF/VEL/VOX	12 wks, $63K				12 wks, $63K				12 wks, $63K			
	Indicated for use after failure of any of the above direct-acting antiviral regimens.											
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.											

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 **GLE**=Glecaprevir **GZR**=grazoprevir **LDV**=ledipasvir **OBV**=ombitasvir **PEGI**=pegylated interferon **PIB**=Pibrentasvir **PTV**=paritaprevir
RBV=ribavirin **RTV**=ritonavir **SIM**=simeprevir **SOF**=sofosbuvir **VEL**=velpatasvir **VOX**= Voxilaprevir

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)

Nov 2019

GENERIC/TRADE	DOSING	TREATMENT DURATION	DOSE REDUCTION / DISCONTINUATION
Ribavirin RBV PL **Ibavyr** 200, 400 ⁶, 600mg ☎ ✆ tab **Moderiba** 200,400,600mg tab **COPEGUS** 200mg cap	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 PL **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 <0.75x10⁹/L → ↓135mcg SC once weekly • Platelets <50x10⁹/L → ↓90mcg SC once weekly • ALT progressively ↑ vs transient flare → ↓90mcg SC once wkly **DISCONTINUE PEGASYS IF:** • ANC<0.5x10⁹/L restart when ANC>1x10⁹/L with 90ug/wk, platelets <25x10⁹/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 PL 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 <0.75x10⁹/L, WBC<1.5x10⁹/L, or platelets <50x10⁹/L:↓ dose to 1mcg/kg/week. If required, ↓ dose again to 0.5mcg/kg/wk. • **Tx naïve non-GT1:** if ANC<0.75x10⁹/L, WBC<1.5x10⁹/L or platelets<80x10⁹/L: ↓ dose to 0.75mcg/kg/week **DISCONTINUE PEGETRON IF:** • ANC<0.5x10⁹/L, WBC <1x10⁹/L, platelets <25x10⁹/L (<50x10⁹/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.

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 73-74). **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]

Other Direct-Acting Antivirals: (sometimes used; additional information) Nov 2019

GENERIC/TRADE	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	DOSING	$/COURSE
Sofosbuvir SOF SOVALDI 400mg tab ☎ ✆	• AE: fatigue, headache, nausea, insomnia, neutropenia, ?cardiac toxicity. CI: monotherapy, unstudied in renal impairment. • DI: P-gp substrate; no statin DI; ↓SOF: anticonvulsants, rifampin, St. John's Wort, tipranavir/ritonavir; amiodarone ↓HR (HR monitoring x 2 weeks required if concomitant use unavoidable).	400mg tablet po once daily. Use only in combo with other agents - see **Indications & Regimens**.(FDA'17: Age ≥12yr GT2,3)	$55,100 12wks
Protease Inhibitors (PI) **Simeprevir SIM** GALEXOS OLYSIO FDA 150mg cap ☎ ✆	• AE: rash sulfa (~28%), photosensitivity, HA, fatigue, ↑ bilirubin (<50%),↑ LFTs (ALT, AST). ASV: anemia, ↓ Plt. • CI: monotherapy, concurrent use of moderate/strong CYP3A4 inhibitors or inducers (see DIs below), decompensated cirrhosis. **Avoid use in prior PI failure** due to concerns of cross-resistance. **Do not use SIM in GT1a if Q80K positive**. • DI: **SIM** inhibits P-gp, OATP: ↑ levels of atorvastatin, digoxin, rosuvastatin. **ASV** inhibits 2D6 (e.g. ↑ levels of flecainide, propafenone, TCAs) & p-gp (e.g. ↑ levels of dabigatran, digoxin). ↓**SIM, ASV**: CYP3A4-inducers (e.g. CBZ, dexamethasone, efavirenz, etravirine, phenytoin, phenobarb, rifampin, SJW). ↑**SIM, ASV:** CYP3A4-inhibitors (e.g. azole antifungals, clarithromycin, cobicistat, erythromycin, HIV protease inhibitors, milk thistle). ↓**ASV:** OATP-inhibitors (e.g cyclosporin, gemfibrozil, rfampin). • M: HCV-RNA at TW4,12 & 24 (discontinue if HCV RNA ≥ 25IU/ml at TW4 or detectable at TW12). **ASV**: monitor LFTs (q2wks x 12 wks, then q4wks).	150mg capsule po once daily with food. Use only in combination with other agents - see **Indications & Regimens**.	$36,600 12 wks
Asunaprevir ASV SUNVEPRA 100mg cap ☎⊗		100mg capsule po twice daily. Use only in combination with other agents- see **Indications & Regimens**.	$13,200 24 wks
Daclatasvir DCV DAKLINZA 30, 60mg tab ☎✆ (D/C USA 2019)	• AE: HA, N/D, fatigue, ↑ lipase. CI: monotherapy. • DI: Inhibits P-gp, OATP: ↑ levels of amiodarone (when with SOF), buprenorphine, colchicine, dabigatran, digoxin, edoxaban. ↓**DCV**: CYP3A4-inducers (e.g. CBZ, dexamethasone, efavirenz, etravirine, phenytoin, phenobarb, rifampin, ritonovir, SJW). ↑**DCV**: CYP3A4-inhibitors (e.g. azole antifungals, clarithromycin, cobicistat).	30-60mg tablet po once daily. May need dose adjustment in presence of inducers/inhibitors. Use only in combination with other agents - see **Indications & Regimens**.	$36,100 12 wks
TECHNIVIE PTV/RTV/OBV 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. Do not chew, break or crush. Ritonavir added to decrease paritaprevir metabolism, allowing once-daily dosing.	$56,000 12wks

Previously Used Direct-Acting Antivirals (no longer recommended, use alternate treatments): Nov 2019

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 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, LFTs, 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 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: 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: 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 < 1log10 ↓ 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, azol 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.

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:** ≥ $2\log_{10}$ ↓ in HCV-RNA at week 12 compared to baseline
- **Delayed VR DVR:** ≥ $2\log_{10}$ ↓ in HCV-RNA but still ≥ 50IU/mL at TW12, then <50IU/mL from TW24 until therapy completed
- **Null Response NR:** < $2\log_{10}$ ↓ in HCV-RNA level at TW12 vs baseline
- **Partial Response PR:** ≥ $2\log_{10}$ ↓ 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

☎=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 **IL28B**=interleukin 28B **LFT**=liver function test **mos**=months **MSM**=men who have sex with men **PI**=protease inhibitor **pt**=patient **PWID**=people who inject drugs **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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Pre-exposure Prophylaxis (PrEP) for HIV: Drug Comparison Chart

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Complete Abbreviations: ♀=female ♂=male =renal dosing may be required ✓=Health Canada Official Indication ✗ =non-formulary in Saskatchewan ⊗=non-formulary for Non-Insured Health Benefits (NIHB) **admin**=administration **AE**=adverse events **ARCH-IDU**=Assessing the Risk of Contracting HIV – Injection Drug Users **ARVs**=antiretroviral **AUD**=alcohol use disorder **BC-CfE**=British Columbia Centre for Excellence in HIV/AIDS **BMD**=bone mineral density **Ca^{++}**=calcium **CBC**=complete blood count **cc**=with food **CDN**=Canadian **CI**=contraindicated **CKD**=chronic kidney disease **CMAJ**=Canadian Medical Association Journal **d**=day **D/C**=discontinue(d) **DI**=drug interaction **dx**=disease **eGFR**=estimated glomerular filtration rate **EtOH**=alcohol **FDA**=approved Food & Drug Admin **FTC/TAF**=emtricitabine/tenofovir alafenamide **FTC/TDF**=emtricitabine/tenofovir disoproxil fumarate g=generic **GI**=gastrointestinal **HA**=headache **HBV**=hepatitis B virus **HCV**=hepatitis C virus **HIRI-MSM**=HIV Incidence Risk Index for MSM **HIV**=human immunodeficiency virus **HPV**=human papillomavirus **hr**=hour **HS**=bedtime **HTN**=hypertension **hx**=history **IAS**=International Antiviral Society **IM**=intramuscular **kg**=kilogram **min**=minute **mL**=millilitres **M**=monitoring **mo(s)**=month(s) **MSM**=men who have sex with men **NIHB**=non-insured health benefits **NNH**=number needed to harm **NNT**=number needed to treat **nPEP**= nonoccupational post exposure prophylaxis **NSAID**=non-steroidal anti-inflammatory drugs **N/V/D**=nausea/vomiting/diarrhea **OUD**=opioid use disorder **PrEP**=pre-exposure prophylaxis **PWID**=people who inject drugs **q**=every **r/o**=rule out **RRR**=relative risk reduction **SCr**=serum creatinine **SK**=Saskatchewan **SPDP**=Sask. Prescription Drug Plan **STI**=sexually transmitted infection **sx**=symptoms **T2DM**=type 2 diabetes mellitus **tab**=tablet **TGW**=transgender woman/women **tx**=treatment **USA**=United States of America **USPSTF**=US Preventive Services Task Force **yr(s)**=year(s)

Online Extras:

HIV Incidence Risk Index for MSM HIRI-MSM: Available at: https://smartsexresource.com/health-providers/provider-tools/calculate-hiri-msm-score

Assessing the Risk of Contracting HIV – Injection Drug Users (ARCH-IDU): Available at: https://www.albertahealthservices.ca/assets/info/hp/srh/if-hp-srh-hiv-prep-guidelines.pdf, see appendix C, page 19.

Saskatchewan Resources:

- **SK HIV Collaborative**: https://skhiv.ca/
- **PrEP Clinics**
  - Regina HIV PrEP Clinic
    - Call for more information or to book your PrEP consultation: 306-766-3935
    - Patient self-refer
  - Saskatoon OUTSaskatoon – Sexual Health Clinic
    - Call for more information or to book an appointment: 306-244-7989
- University of Saskatchewan Student Wellness Centre

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HIV Chart

Complete Abbreviations ✓= Health Canada Official Indication ς =scored tablet ✗ =Non-formulary Sask ☎=Exception Drug Status SK ✆ =prior approval for NIHB ⊗=not covered by NIHB ▼=covered by NIHB ♀=female ♂=male ◎=fixed dose combination product **A1c**=glycosolated hemoglobin **ac**=before meals **ACR**=albumin:creatinine ratio **AE**=adverse effects **HR**=Hazard Ratio **AST**=asparate aminotransferase **ALT**=alanine aminotransferase **BC-CfE**=British Columbia Centre for Excellence in HIV/AIDS **BID**=twice daily **BMD**=bone mineral density **BP**=blood pressure **cap**=capsule **CBC**=complete blood count **CBZ**=carbamazepine **cc**=with food **CCB**=calcium channel blocker **CI**=contraindication **CKD**=chronic kidney disease **CMV**=cytomegalovirus **CNS**=central nervous system **CrCl**=creatinine clearance **CV**=cardiovascular **CW**=Choosing Wisely **CXR**=chest x-ray **d**=day **D/C**=discontinue(d) **DHHS**=Department of Health & Human Services **DI**=drug interaction **DOAC**=direct oral anticoagulant **dx**=disease **EACS**=European AIDS Clinical Society Guidelines **EDS**=exception Drug Status **eGRF**=estimated glomerular filtration rate **FBG**=fasting blood glucose g=generic **GI**=gastrointestinal **H2RA**=histamine 2 receptor antagonists **HA**=headache **HAV**=hepatitis A virus **HBsAg**=Hep B "surface" antigen **HBV**=hepatitis B virus **HCV**=hepatitis C virus **Hgb**=haemoglobin **HIV**=human immunodeficiency virus **HPV**=human papillomavirus **HS**=bedtime **HTN**=hypertension **hx**=history **IAS**=International Antiviral Society **ID**=Infectious Disease(s) **IGRA**=interferon gamma release assay **INSTI**=Integrase Strand Transfer Inhibitor **LDL**=low density lipoprotein **LFT**=liver function tests **lytes**=electrolytes **MAC**=mycobacterium avium complex **mg**=milligrams **mL**=millitres **MMR**=measles, mumps, rubella **MSM**=men who have sex with men **mo(s)**=month(s) **N/V/D**=nausea/vomiting/diarrhea **NRTI**=nucleos(t)ide reverse transcriptase inhibitor **NNRTI**=non-nucleoside reverse transcriptase inhibitor **NNT**=number needed to treat **nPEP**=nonoccupational post exposure prophylaxis **oPEP**=occupational post exposure prophylaxis **OI**=opportunistic infection **OTC**=over the counter **PCP/PJP**=Pneumocystis jiroveci/carinii pneumonia **PDE5i**= phosphodiesterase-5 inhibitor **PEP**=post exposure prophylaxis **PI**=protease inhibitor **PK**=pharmacokinetics **po**=oral **PPI**=proton pump inhibitor **PrEP**=pre-exposure prophylaxis **Pt(s)**=patient(s) **PWID**=people who inject drugs **q**=every **QOL**=quality of life **r/o**=rule out **SAP**=Special Access Program **SCr**=serum creatinine **SJW**=St. John's Wort **SK**=Saskatchewan **SOGC**=Society of Obstetricians and Gynaecologists of Canada **soln**=solution **SPDP**=Sask. Prescription Drug Plan **STI**=sexually transmitted infection **T2DM**=type 2 diabetes mellitus **tab**=tablet **TAF**=tenofovir alafenamide **TB**=Tuberculosis **TDF**=tenofovir disoproxil fumarate **TGW**=transgender woman/women **TMP/SMX**=cotrimoxazole or sulfamethoxazole/trimethoprim **TST**=tuberculin skin test **tx**=treatment **U=U**: Undetectable=Untransmittable **VZV**=varicella zoster virus **WHO**=World Health Organization **wk(s)**=week(s) **Wt**=weight **yr(s)**=year(s)

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HIV Chart online extras:

Table 2. Opportunistic Infection (OI) Primary Prophylaxis

Opportunistic Infection	CD4	Start Prophylaxis	D/C Prophylaxis
PCP *(aka PJP)*	<200	TMP/SMX 80/400mg daily	CD4 >200 x ≥3mons
Toxoplasmosis	<100	TMP/SMX 160/800mg daily	CD4 >200 x ≥3mons
MAC *(not usually required if starting ART ASAP)*	<50	Azithromycin 1250mg weekly	CD4 >100 x ≥3mons

- **Tuberculosis** may occur at any CD4 count & screening is required CXR, TST or IGRA, see above
- **Candidiasis Treatment**: **oropharyngeal**: nystatin, fluconazole; **esophageal**: fluconazole

- *Most* patients require 3 active antiretrovirals → 2 NRTIs + 3rd agent (INSTI or boosted PI or NNRTI).
  Note: PK booster (i.e. ritonavir & cobicistat available Canada as combo products ◎) are not considered active ARVs.

NRTI Backbone
(choose 1 combo product which contains 2 NRTIs)
- **TRUVADA or**
- **DESCOVY or**
- **KIVEXA**

+

3rd Agent *(choose 1 agent from 1 class)*
- **INSTI: DTG, BIC, RAL, EVG* or**
- **PI: DRV‡, ATV‡ or**
- **NNRTI: RPV, DOR, EFV** (NNRTIs not 1st line)

PK boosters: *add **COBI**; ‡add **RTV** or **COBI**

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BIKTARVY	**108**
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Amprenavir	110
APTIVUS	110
Atazanavir	110
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Cabotegravir	110
Cobicistat	110
Darunavir	110
Didanosine	110
Dolutegravir	110
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EDURANT	110
Efavirenz	110
Elvitegravir	110
Emtricitabine	110
EMTRIVA	110
Etravirine	110
Fosamprenavir	110
HIV	110
INSTI	110
INTELENCE	110
INVIRASE	110
ISENTRESS	110
KALETRA	110
Lamivudine	110
LEXIVA	110
Lopinavir	110
Nelfinavir	110
Nevirapine	110
NORVIR	110
PIFELTRO	110
PI-HIV	110
PREZCOBIX	110
PREZISTA	110

Protease Inhibitor	110
Raltegravir	110
RETROVIR	110
REYATAZ	110
Rilpivirine	110
Ritonavir	110
Saquinavir	110
Stavudine	110
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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%.
2) Amantadine Dosing Adjustments for Age and Renal Function

AMANTADINE -*SYMMETREL* Dosage by Age & Renal Function [i,ii] { Note, no longer recommended for influenza prophylaxis due to resistance.}

No recognized renal dysfunction	TREATMENT DOSAGE	
Children 1-9 yrs [a]	5mg/kg daily or divided BID (total daily dose not to exceed 150mg)	
Children >10 yrs	200mg daily or divided BID [b] (if less than 40 kg, give 5mg/kg per day)	
Adults ≤ 64 yrs	200mg daily (or 100mg BID) [b] (Note: **100mg daily** adequate/better tolerated for **prophylaxis**)	
Adults ≥ 65 yrs	100mg daily	
Renal dysfunction: CrCl * in ml/second (ml/min in brackets)		**Alternate dosing adjustment schedule[2]**
>1.33ml/s (80-99 ml/min)	100mg po daily	100mg Day 1, 100mg/day start Day 2
1.00-1.32 ml/s (60-79 ml/min)	Alternating daily doses of 100mg & 50mg	100mg Day 1, 75mg/day start Day 2
0.67-0.99 ml/s (40-59 ml/min)	100mg every 2 days	100mg Day 1, 50mg/day start Day 2
0.50-0.66 ml/s (30-39 ml/min)	100mg twice weekly	100mg Day 1, 25mg/day start Day 2
0.33-0.49 ml/s (20-29 ml/min)	50mg three times per week	
<0.32 ml/s (10-19 ml/min)	Alternating weekly doses of 100mg & 50mg	If outbreak continues, repeat 100mg dose every 7 days during outbreak.
Hemodialysis	200mg every 7 days	

* **Calculation of creatinine clearance: CrCl** $_{ml/second}$ = {(140-age) x weight (kg)} / {serum creatinine (umol/L) x 50} ◆ Female: CrCl = 0.85 x CrCl (male)

[a] **Use in children** < 1yr old has not been evaluated

[b] **Patients with history of seizures**: consider reduction in amantadine dose (<100mg daily) or use alternate neuraminidase inhibitor

AFLURIA	111
Amantadine	111
FLUAD	111
FLUCELVAX	111
FLULAVAL	111
FLUMIST	111
FLUVIRAL	111
FLUZONE	111
Influenza	111
INFLUVAC	111
M2 Inhibitor	111
Neuraminidase Inhibitor	111
Oseltamivir	111
Peramivir	111
RAPIVAB	111
RELENZA	111
SYMMETREL	111
TAMIFLU	111
Vaccine	111
Zanamivir	111
Baloxavir	111
XOFLUZA	111

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Since the 2011-12 influenza season, NACI has recommended that egg-allergic individuals may be vaccinated against influenza using TIV, without a prior influenza vaccine skin test, based on an assessment of risk for a severe allergic reaction to guide the method of vaccination. (NACI recommendation Grade A)Footnote bb Details of the vaccine delivery protocols are found below. Because of the lack of data, the use of FluMist® in egg-allergic persons is not recommended at this time. However, ovalbumin concentrations in FluMist® are documented to be very low and a study is currently underway to assess the use of FluMist® in egg-allergic persons. Its use will be re-evaluated when further data become available. Although ovalbumin content in influenza vaccine manufactured in eggs may vary from year to year, between vaccine products or between lots of the same vaccine,[Footnote 6363-Footnote 6565] vaccines marketed in Canada are approved under the European specification for ovalbumin content, which is currently <1.2 µg/mL, the level associated with low risks of adverse events.[Footnote 6666] An egg-allergic individual is considered to be at higher risk for severe allergic reactions by CSACI if they have had a previous respiratory or cardiovascular reaction or generalized hives when exposed to egg, or have poorly controlled asthma. Two vaccine delivery protocols can be used for egg-allergic 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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No other federal system to date has detected a statistically significant association between GBS and 2009 H1N1 vaccination. Surveillance and further analyses are ongoing. The 2009 H1N1 vaccine safety profile is similar to that for seasonal influenza vaccines, which have an excellent safety record. Vaccination remains the most effective method to prevent serious illness and death from 2009 H1N1 influenza infection; illness from the 2009 H1N1 influenza virus has been associated with a hospitalization rate of 222 per 1 million and a death rate of 9.7 per 1 million population.

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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/

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. rhuematoid 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

Tafenoquine **ARAKODA/KRINTAFEL**	FDA'18: to **prevent relapse** of Plasmodium vivax malaria in ≥16 yrs who are receiving appropriate antimalarial therapy for acute P vivax infection & off-label for P. ovale, plus in ≥18 yrs for **prophylaxis of malaria**: Loading regimen: For each of the 3 days before travel to a malarious area give 200 mg (2 of the 100 mg tablets) once daily for 3 days; Maintenance regimen: While in the malarious area give 200 mg (2 of the 100 mg tablets) once weekly – start 7 days after the last loading regimen dose; Terminal prophylaxis regimen: In the week following exit from the malarious area give 200 mg (2 of the 100 mg tablets) taken one time, 7 days after the last maintenance dose. Give with food; CI: G6PD deficiency, psychotic disorders, pregnancy.

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:

Artesunate IV: investigational in the USA for initial treatment of severe malaria (children and adults). 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. RCTs show a reduction in mortality compared to IV quinine. Not active against hypnozoite liver stage forms of *Plasmodium (vivax and ovale).* Treatment should be followed by a full course of an oral antimalarial regimen.
Artemisinin based combo therapies: for uncomplicated malaria; potential advantage is the killing of the younger circulating stages of *P. falciparum* before they sequester; however resistance seen in some areas. Counterfeit products are a problem. .

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.

ARAKODA	112
ARALEN	112
Atovaquone/Proguanil	112
Chloroquine	112
DEET	112
DOXYCIN	112
Doxycycline	112
Icaridin	112
KRINTAFEL	112
LARIAM	112
Malaria	112
MALARONE	112
Mefloquine	112
MUSKOL	112
NATRAPEL	112
OFF	112
Picaridin	112
Plasmodium	112
Primaquine	112
Tafenoquine	112
WATKINS	112

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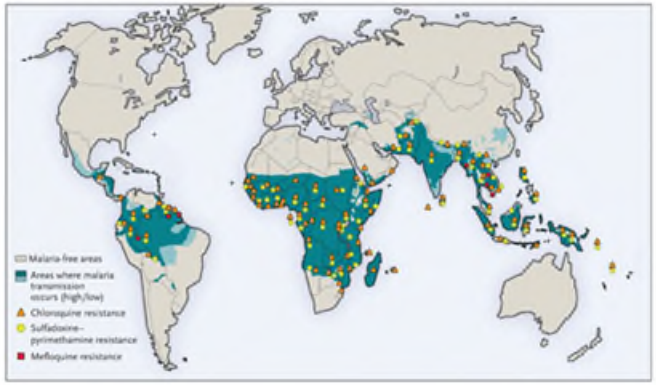

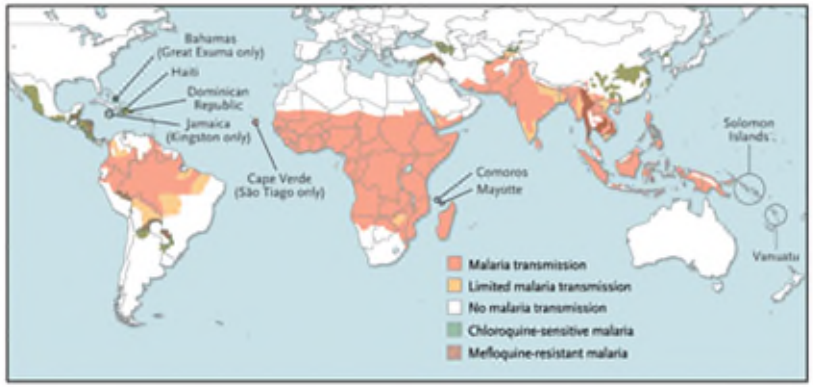

Thumbnails: Areas of Malaria Transmission and Antimalarial Drug Resistance. Data on malaria transmission are for 2007 and are from the World Health Organization. Data on drug resistance are for 2004 and are from the Roll Back Malaria partnership.**NEJM** June 5,2008. 2nd Map Thumbnail: NEJM Aug 7, 2008.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

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Centers for Disease Control and Prevention
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www.cdc.gov/vaccines/vpd-vac/flu/default.htm (influenza vaccine)

National Foundation for Infectious Disease
www.nfid.org/pdf/factsheets/pneuadult.pdf

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See online Extras for SMART-COP

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	+1
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$_2$sat ≤90% or PaO$_2$/FiO$_2$ < 333 > 50 yr: PaO$_2$ < 70 mmHg or O$_2$sat ≤93% or PaO$_2$/FiO$_2$ < 250	+2
pH <7.35	+2

Interpretation

Total Points	IRVS 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

CRB-65	116
CURB-65	116
Pneumonia	116
Pneumonia Risk score	116
PSI Algorithm	116
SMART-COP	116
SOAR	116

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URINARY TRACT INFECTIONS (UTI), ABBREVIATION LIST:

=online extras =scored tab =↓ dose for renal dysfunction; = Exception Drug Status Sask. ✗ =non-formulary in SK ▼=covered by NIHB =prior NIHB ♀ =female ♂=male **ABX**=antibiotic **AE**=adverse events **Alt**=alternate **AMG**=aminoglycoside **cc**=with food **CI**=contraindication **CrCl**=creatinine clearance **C&S**=culture & sensitivity **CEPH**=cephalosporins **CUA**=Canadian Urological Association ***E.coli***= *Escherichia coli* **d**=day(s) **DBW**=dosing body weight **DM**=diabetes mellitus **DS**=double strength (1DS tab= 160/800mg) **ESBL**=extended spectrum beta-lactamases **FQ**=fluoroquinolones **Fx**=function **g**=generic drug available **G6PD**= glucose-6-phosphate dehydrogenase **GI**=gastrointestinal **Gm –ve**= gram negative **HA**=headache **HS**=bedtime **IBW**=ideal body weight **IDSA**=Infectious Diseases Society of America **IV**=intravenous **mos**=month(s) ***P.aeruginosa***= *Pseudomonas aeruginosa* **po**=oral **pt**=patient **q**=every **Rx**= prescription **SAE**=serious advere events **SCI**=spinal cord injury **SK**=Sask **SOGC**=Society of obstetricians and Gynaecologists of Canada **sx**=symptom(s) **tx**=Treatment **TMP/SMX**=trimethoprim/sulfamethoxazole **UTI**=urinary tract infection **wk(s)**=week(s) **yr**=year

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URINARY TRACT INFECTIONS (UTI)

Prepared by: Loren Regier; Updated by: Marlys LeBras © ***www.RxFiles.ca*** **May/20**

1. Probable Organisms in UTIs

- **Acute uncomplicated cystitis in otherwise healthy ♀:** *E. coli*$_{(non\text{-}ESBL)}$ 75-95%, other *Enterobacterales* organisms (e.g. *Klebsiella* species, *Proteus mirabilis*), *S. saprophyticus*
  - ≥ 95% of episodes are caused by a single bacterial organism
- **Complicated UTI:** *E. coli,* other *Enterobacteriaceae* organisms (e.g. *Klebsiella* species*, Proteus* specie)*, Enterococci, P. aeruginosa*
  - Episodes may be caused by multiple organisms; increase risk of antibiotic-resistent organsisms due to repeated antimicrobial courses and/or presence of instrumentation.
- **Pyelonephritits:** *E. coli,* other *Enterobacteriaceae* organisms (e.g. *Klebsiella* species, *Proteus mirabilis*), *S. saprophyticus*
- **Prostatitis:** *E. coli,* other *Enterobacteriaceae* organisms (e.g. *Klebsiella* species, *Proteus mirabilis*), *Enterococci, P. Aeruginosa.*
  If risk factors for STI (e.g. sexually active & age <35, or multiple sexual partners) consider treatment for N.gonnorrhoeae, C.trachomatis, trichomonas
- **Note:** Group B *Streptococcus* (*S. agalactiae)* may be present in those with diabetes or pregnancy

2. Oral Antimicrobials Spectrum of Activity for UTIs

Nitrofurantoin (e.g. MACROBID): *E. coli. Klebsiella* species*, S. saprophyticus, Enterococcus faecalis, ESBL*
- No coverage of: *Proteus* species*, Pseudomonas* species

SMX/TMP: *E. coli, Klebsiella* species*, P. mirabilis, S. saprophyticus*
- No coverage of: *Enterococci, Pseudomonas* species

Ciprofloxacin: *E. coli, Klebsiella* species*, P. mirabilis, S. saprophyticus, Pseudomonas* species, *Enterococcus faecalis*
- No coverage of: *Enterococcus faecium*

Fosfomycin: *E. coli, Klebsiella* species*, P. mirabilis, Enterococci, Pseudomonas* species, *ESBLs*

Amoxicillin/Clavulanate: *E. coli, Klebsiella* species*, P. mirabilis, S. saprophyticus, Enterococcus faecalis*
- No coverage of: *Pseudomonas* species, *Enterococcus faecium*

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Evidence Summary Table for Nitrofurantoin RCTs- not comprehensive

Author	Treatment	Control	Population	Bacterial Cure	Clinical Cure	Harm	Comments
Gupta et al. (2007) n=338	Nitrofurantoin monohydrate / macrocrystals, MACROBID 100mg BID **for 5 days**	TMP/SMX 160/800 mg BID for 3 days	Females with a median **age of 21** (18-41), 82% of isolates were *E. coli* alone, 4% *E. coli* in combination with another uropathogen, 8% *S. saprophyticus*, or enterococci, *Klebsiella* species, *P. mirabilis, Enterobacter* species, or group B streptococci (1%-3% each)	5-9 days after therapy: 141/154 (92%) vs 131/144 (91%) Risk difference -1 (95% CI, -7 to 6%) [NS]	5-9 days after therapy: 144/160 (90%) vs 133/148 (90%) Risk difference -1 (95% CI, -7 to 6) [NS] 30 days after therapy: 134/160 (84%) vs 117/148 (79%) Risk difference -5 (95% CI, -13% to 4%) [NS]	2% of nitrofurantoin and 1% of TMP/SMX participants left the study due to adverse effects [NS]	- **No difference in clinical or bacterial cure rates, or AE.** - Clinical cure was defined as women who didn't require antimicrobial drug treatment for lack of resolution of initial UTI symptoms or for new UTI symptoms within 30 days following the initiation of treatment. - n=7/17 (41%) of women with a TMP/SMX non-susceptible uropathogen had a clinical cure. - The most common adverse effects experienced were nausea, diarrhea, headache, light-headedness, & vaginal itching. - 39% vs 41% of patients experienced ≥ 1 adverse effect when questioned about specific symptoms [NS]. - 6% vs 11% required OTC treatment of AEs [NS].
Stein et al. (1999) n=749	Nitrofurantoin monohydrate / macrocrystals, MACROBID 100mg BID **for 7 days**	Fosfomycin single 3-g dose	Females with a median **age of 33** (15-92), approximately 82% of isolates were *E. coli*, 5% *P. mirabilis,* 5% *K. pneumoniae,* 4% *S. saprophyticus,* 4% other	4-6 weeks after therapy: 112/102 (91%) vs 120/125 (96%) (95% CI, -11 to 1.3%) P=0.18 [NS]	4-6 weeks after therapy: 165/180 (92%) vs 184/202 (91%) (95% CI, -5.1 to 6.2%) P=0.91 [NS] note: NS after 5-11 days after initial dose & 5-11 days after therapy	4.3% of nitrofurantoin & 1.9% of fosfomycin participants left study due to AE that were not medically severe (P=0.06) [**SS**] NNH=42	- **No difference in clinical cure rates or bacterial cure rates. More patients withdrew from study with nitrofurantoin due to adverse effects (NNH=42).** - Clinical cure was defined as elimination of all pre-therapy symptoms at 4-6 weeks following the last dose of medication. - Most common adverse effects experienced were nausea, vaginitis, dizziness and diarrhea. - 5.6 % vs 5.3% of patients experienced probable drug related AE as assessed via open-ended interview [NS].
Iravani et al. (1999) n=521	Nitrofurantoin monohydrate / macrocrystals, MACROBID 100mg BID **for 7 days**	Ciprofloxacin 100 mg BID **for 3 days** TMP/SMX 160/800 mg BID **for 7 days**	Females with an average **age of 34** (19-85), total microbiologic picture was not reported	4-10 days after therapy:* NTF: 153/177 (86%) Cipro: 148/168 (88%) TMP/SMX: 161/174 (93%) 4-6 weeks after therapy: NTF: 115/141 (82%) Cipro: 118/130 (91%) TMP/SMX: 113/144 (79%) TMP/SMX vs Cipro: [**SS**] NNT=9 (95% CI, -20.6% to -3.9%) NTF vs Cipro: [**SS**] NNT=12 (95% CI, -17.1% to -0.9%)	4-10 days after therapy: * NTF: 166/179 (93%) Cipro: 160/168 (95%) TMP/SMX: 165/174 (95%) 4-6 weeks after therapy:* NTF: 135/151 (89%) Cipro: 132/147 (90%) TMP/SMX: 137/153 (90%) *[NS between agents]	Premature discontinuation due to AE: TMP/SMX n=11, NTF n=7, cipro n=3 [NS]	- **No difference in clinical cure rates. Greater bacterial cure rates with ciprofloxacin vs TMP/SMX or NTF at 4-6 weeks** NNT=9,12 respectively**, but no difference at 4-10 days after therapy. More overall AE with TMP/SMX vs cipro (p<0.05, rates aren't reported).** - Clinical cure was defined as resolution (i.e. disappearance of signs and symptoms related to the infection such that additional antimicrobial therapy was not required). - Most common adverse effects experienced were nausea, vaginitis, dizziness and diarrhea
Hooton et al. (1995) n=164	Nitrofurantoin macrocrystalline, MACRODANTIN 100 mg QID **for 3 days**	TMP/SMX 160/800 mg BID Cefadroxil 500 mg BID	Females with an average **age of 24** (range NR), 85% of isolates were *E. coli*, 5% other	4-6 weeks after therapy: Nitrofurantoin: 22/36 (61%)* TMP/SMX: 32/39 (82%)* Cefadroxil: 21/32 (66%) Amoxicillin: 28/42 (67%)		Adverse effects leading to discontinuation of treatment occurred in 5	- **Nitrofurantoin 3 days was INFERIOR to TMP/SMX 3 days for clinical/bacterial cure (NNH=5). There was no difference in AE.** - Cure was defined as the resolution of symptoms and eradication of significant bacteriuria (≥10^2 CFU/mL) at

		Amoxicillin 500 mg TID [**all for 3 days**]	Enterobacteriaceae, 3% *S. saprophyticus,* 6% other gram positive cocci	*Risk difference 21% (95% CI, 1-41%) p=0.04 [**SS**] NNH=5 all other comparisons were [NS]		patients (n=3 cefadroxil, n=1 amoxicillin, & n=1 TMP/SMX) [NS]	4-6 weeks. - Most common adverse effects experienced were vaginitis, nausea, headache, & diarrhea. - AE 43% nitrofurantoin, 35% TMP/SMX, cefadroxil 30%, 25% amoxicillin [NS]
Christiaens et al. (2002) n=78	Nitrofurantoin macrocrystalin, 100mg QID **for 3 days**	Placebo, QID for 3 days	Females with a median **age of 30** (15-54), microbiologic picture was not reported	Day 7: 17/23 (74%) vs 9/22(41%) P=0.1 [**SS**] NNT=4	Day 7: 24/40 (60%) vs 14/38 (37%) P=0.04 [**SS**] NNT=5	Adverse effects leading to discontinuation of treatment occurred in one participant in the placebo group [NS]	- **Nitrofurantoin was superior to placebo in clinical cure and bacterial cure rates.** - Clinical cure is defined as asymptomatic at 7 days following initiation of treatment. - Most common adverse effects experienced were gastrointestinal problems, headache, & dizziness/fatigue. - 23% vs 26% patients experienced adverse effects as recorded in a diary [NS].
Huttner et al. (2018) n=513	Nitrofurantoin macrocrystalline 100mg TID x 5 days	Fosfomycin 3g sachet x 1 dose	Females with an average **age of 44** (IQR 31-64), ~60% of isolates were *E. coli*, ~20% other Enterobacteriaceae	Day 28 129/175 (74%) vs 103/163 (63%) P=0.04 [**SS**] NNT=9	Day 28 171/244 (70%) vs 139/241 (58%) P=0.004 [**SS**] NNT=9	Adverse effects leading to discontinuation of treatment n=1 nitrofurantoin, n=0 fosfomycin	- **Nitrofurantoin was SUPERIOR to fosfomycin for clinical/bacterial cure. There was no difference in AE.** - Clinical Cure was defined as complete resolution of symptoms and signs of UTI without prior failure i.e. need for additional or change in antibiotic treatment due to a UTI or discontinuation due to lack of efficacy - Most common adverse effects experienced were GI - 8% vs 6% reported ≥ 1 AE - Excluded patients CrCl <30mL/min

Evidence Summary Table for Nitrofurantoin and Reduced Renal Function Beers Recommendation

Author	Design	Population	Clinical cure	Harm	Comments
Geerts et al. (2013) n=21,317	Population-level, retrospective cohort study. Adult ♀ with a UTI prescribed nitrofurantoin for 3-9 days were included. Dutch community pharmacy, family physician, and hospital databases from 2005-10 were utilized.	~48 yr (18-103 yr); 100% ♀; ~80% tx duration 4-5 days; eGFR 83 mL/min/1.73m^2 (9-200 mL/min/1.73m^2); 0.9% eGFR <50 mL/min/1.73m^2; 82% unknown eGFR	>80 mL/min/1.73m^2 (reference): 1,568/1,859 (84%) 50-80 mL/min/1.73m^2: 1,528/1,842 (83%) vs reference aHR 0.92 (95% CI, 0.78 to 1.08) [NS] 30-49 mL/min/1.73m^2: 131/166 (79%) vs reference aHR 1.06 (95% CI, 0.74 to 1.51) [NS] 10-29 mL/min/1.73m^2: 14/20 (70%) vs reference aHR 1.57 (95% CI, 0.7 to 3.52) [NS] <10 mL/min/1.73m^2: 1/1 (100%) vs reference data not available	Serious AE: n=34 in total of which n=33 were pulmonary reactions (n=28 unspecified chest pain, n=3 painful respiration, n=1 pleural effusion) & n=1 hemolytic anemia ≥50 mL/min/1.73m^2 (reference): 13/3,701 (0.35%) <50 mL/min/1.73m^2: 4/187 (2.14%) vs reference aHR 4.13 (95% CI, 1.31 to 13.09) unknown eGFR: 17/17,429 (0.1%)	- **Similar clinical cure rates, but more SAE with impaired renal function.** - Clinical cure was defined as no initiation of a second antibacterial for treatment of UTI other than nitrofurantoin or TMP respectively within 1 month after the start of a course of nitrofurantoin. - Serious AE was defined as AE leading to hospitalization within 90 days after the start of a course of nitrofurantoin therapy. - HR were calculated and adjusted for age ± use of blood glucose-lowering drugs.
Bains et al. (2009)	Retrospective review. Patients with suspected UTI who	~75 yr (4-103 yr); ~75% ♀; ~36% impaired renal	Impaired renal function (≤50 mL/min) 71% (95% CI, 63-79%) vs	No reports of serious AE (i.e. peripheral neuropathy, acute pulmonary reaction)	- **Similar clinical cure rates and AE in normal and impaired renal function groups.** - Clinical cure was defined as treatment discontinuation

n=356	received nitrofurantoin between 2004-08 in Vancouver Island Health Authority were included.	function with mean CrCl of ~40 mL/min (15-50 mL/min) Majority of patients were treated with MACROBID 100 mg PO BID x ~7 d	Control (>50 mL/min) 78% (95% CI, 73-84%) -statistical analysis comparing groups not completed		after an appropriate course of antibiotics (between 5 and 10 days) with no other UTI antibiotics initiated within 14 days and no UTI symptoms (dysuria, urinary frequency, fever, rigors, flank pain, nausea). - Primary outcome was calculated with the MCG equation. Results were similar to the Elderly-Adjusted MCG and MDRD equation. - GI disturbance or headache was reported in 7% of those with impaired renal function vs 8% in control [NS].

Links:
RxFiles UTI Treatment Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-UTI-Tx.pdf

Amoxicillin/Clavulanate	120
BACTRIM	120
Cephalexin	120
CIPRO	120
Ciprofloxacin	120
CLAVULIN	120
COTRIMOXAZOLE	120
Cystitis	120
Fosfomycin	120
KEFLEX	120
LEVAQUIN	120
Levofloxacin	120
MACROBID	120
MACRODANTIN	120
MONUROL	120
Nitrofurantoin	120
Norfloxacin	120
NOROXIN	120
SEPTRA	120
Sulfamethoxazole	120
Trimethoprim	120
Urinary Tract Infection	**120**
UTI	**120**
BACTRIM	121
Cephalexin	121
CIPRO	121
Ciprofloxacin	121
COTRIMOXAZOLE	121
KEFLEX	121
MACROBID	121
MACRODANTIN	121
Nitrofurantoin	121
Post-coital	121
Prophylaxis	121
Sulfamethoxazole	121
Trimethoprim	121
Asymptomatic Bacteriuria	120

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A ABX Comparison – Expanded Chart o http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-ABX-Expanded.pdf

B What is the risk of peripheral neuropathy with nitrofurantoin (MACROBID)? http://www.rxfiles.ca/rxfiles/uploads/documents/Nitrofurantoin-Peripheral-Neuropathy.pdf

What is the risk of pulmonary toxicity with nitrofurantoin (MACROBID)? http://www.rxfiles.ca/rxfiles/uploads/documents/Nitrofurantoin-Pulmonary-Toxicity.pdf

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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
  - Know 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). May consider tamper resistant formulation.
- **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 consent & agreement** for all; (don't assume patients know) (concept of "universal precautions" in pain medicine[vi])
  - Roll for **naloxone kit(s)** to have on hand in event of overdose.
- **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, especially related to CNCP:

- 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).
- When appropriate for the patient, 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 up-front **exit strategy!** Inform patient that an unsuccessful trial (lack of benefit &/or emerging harm/risk) will result in a gradual tapering of the drug before stopping.
- **Acute Pain: consider the usual course/timeline** for physiologic structural healing and pain resolution and titrate/reduce/discontinue pain meds accordingly.
  - For example, what generally happens with this type of acute tissue injury at e.g. 24 hours, 72hours, 1-2weeks, 3-6 weeks, 3 months
  - For example guidance on **post-op quantities**, see Michigan Open link.
- Take a multidisciplinary **team approach** whenever dealing with the problem of misuse & diversion of prescription drugs.[vii] ***Don't abandon the patient!***

Thanks to our original reviewers: Dr. M. Opdahl (FP, SHR Pain Centre), Dr. K. Stakiw (FP, SHR Pall Care), Dr. A. Furlan (Physiatrist, ON), Dr. J. Cross (FP, Emerg physician, SK), D. Spitzig (Pharmacist, CPSS, SK). L Regier BSP, P Butt (MD, CCFP), A Carter (BSP, PharmD Cand.)

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 Guidelines** Use of Opioids for Chronic Non-Cancer Pain , 2017. Accessed at: http://nationalpaincentre.mcmaster.ca/guidelines.html
6) **Opiod Risk Tool** (ORT): Accessed at: http://nationalpaincentre.mcmaster.ca/opioid/cgop_b_app_b02.html {Alternately: CAGE-AID: http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/9-cageform.pdf }
7) **Opioid Taper Template**: http://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Taper-Template.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

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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

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Opioid Risk Tool	122
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Palliative Pain	122
Treatment Agreement	122
Urine Drug Screen	122

References: **Pain Approaches: Acute/Palliative/CNCP chart**

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RxFiles Opioid/Pain Related Links: www.RxFiles.ca/PainLinks

RxFiles 2017 Pain Management and Opioids Newsletter (& Pain Mini-Book)
http://www.rxfiles.ca/rxfiles/uploads/documents/Opioids-Pain-2017-Newsletter.pdf

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Thank you Dr. Marwah for contributing to the review of this chart.

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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.
- Cyclobenzaprine is a TCA like drug, with typical sedation, dry mouth, etc. It's effect is often thought to be primarily related to sedation. Watch out for overuse as harms may easily outweigh benefits.

Acetaminophen	125
Amitriptyline	125
Analgesia	125
Baclofen	125
BOTOX	125
Capsaicin	125
Carbamazepine	125
Chronic Non-Cancer Pain	**125**
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Divalproex	125
Duloxetine	125

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Gabapentin	**125**
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Medication Overuse Headache	**125**
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ZYTRAM	126
Chronic Pain	125
Chronic Pain	126
Pain	126

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

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

Cohen SP, Bhatia A, Buvanendran A, et al. Consensus Guidelines on the **Use of Intravenous Ketamine Infusions for Chronic Pain** From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018 Jul;43(5):521-546.

Cohen SP, Mao J. **Neuropathic pain: mechanisms** and their clinical implications. BMJ. 2014 Feb 5;348:f7656.

Cohen SP, Hanling S, Bicket MC, et al. **Epidural steroid injections compared with gabapentin** for **lumbosacral radicular pain**: multicenter randomized double blind comparative efficacy study. BMJ. 2015 Apr 16;350: h1748.

Collado-Mateo D, Dominguez-Munoz FJ, Adsuar JC, et al. Effects of **Exergames** on Quality of Life, Pain, and Disease Effect in Women With **Fibromyalgia**: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2017 Sep;98(9):1725-1731

Cole BJ, Karas V, Hussey K, et al. **Hyaluronic Acid Versus Platelet-Rich Plasma**: A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of **Knee Osteoarthritis.** Am J Sports Med. 2017 Feb;45(2):339-346.

Collin SM, Norris T, Nuevo R, et al. **Chronic Fatigue Syndrome** at Age 16 Years. Pediatrics. 2016 Jan 25.

Colvin LA, Bull F, Hales TG. **Perioperative opioid analgesia**-when is enough too much? A review of opioid-induced tolerance and hyperalgesia. Lancet. 2019 Apr 13;393(10180):1558-1568.

Colwill AC, Alton K, Bednarek PH, et al. **Cannabinoids for Pain Control** During Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2020;135(6):1289-1295.

Concoff A, Sancheti P, Niazi F, et al. The efficacy of multiple versus single hyaluronic acid injections: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2017 Dec 21;18(1):542.

Cooper TE, Wiffen PJ, Heathcote LC, et al. **Antiepileptic drugs** for chronic non-cancer pain in **children** and **adolescents**. Cochrane Database Syst Rev. 2017 Aug 5;8:CD012536. This review identified only two small studies, with insufficient data for analysis.As we could undertake no meta-analysis, we were unable to comment about efficacy or harm from the use of antiepileptic drugs to treat chronic non-cancer pain in children and adolescents. Similarly, we could not comment on our remaining secondary outcomes: Carer Global Impression of Change; requirement for rescue analgesia; sleep duration and quality; acceptability of treatment; physical functioning; and quality of life.We know from adult randomised controlled trials that some antiepileptics, such as gabapentin and pregabalin, can be effective in certain chronic pain conditions.We found no evidence to support or refute the use of antiepileptic drugs to treat chronic non-cancer pain in children and adolescents.

Corcoran KL, Bastian LA, Gunderson CG, et al. Association Between **Chiropractic Use and Opioid Receipt Among** Patients with Spinal Pain: A Systematic Review and Meta-analysis. Pain Med. 2019 Sep 27.

Corsi DJ, Hsu H, Fell DB, et al. Association of **Maternal Opioid Use** in Pregnancy With Adverse Perinatal Outcomes in Ontario, Canada, From 2012 to 2018. JAMA Netw Open. 2020;3(7):e208256.

Costa ACC, de Lima Benzi JR, Yamamoto PA, et al. Population **pharmacokinetics of gabapentin** in patients with neuropathic pain: Lack of effect of diabetes or glycaemic control. Br J Clin Pharmacol. 2020 Oct 28. doi: 10.1111/bcp.14594.

Cramer H, Klose P, Brinkhaus B, et al. Effects of **yoga on chronic neck pain**: a systematic review and meta-analysis. Clin Rehabil. 2017 Nov;31(11):1457-1465.

Cruccu G, Di Stefano G, Truini A. **Trigeminal Neuralgia**. N Engl J Med. 2020;383(8):754-762

Cruccu G, Finnerup NB, Jensen TS, et al. **Trigeminal neuralgia**: New classification and diagnostic grading for practice and research. Neurology. 2016 Jul 12;87(2):220-8.

Cummings M, Hróbjartsson A, Ernst E. Should doctors recommend **acupuncture for pain**? BMJ. 2018 Mar 7;360:k970.

da Costa BR, Nuesch E, Kasteler R, et al. **Oral or transdermal opioids for osteoarthritis** of the knee or hip. Cochrane Database Syst Rev. 2014 Sep 17;9:CD003115. The small mean benefit of non-tramadol opioids are contrasted by significant increases in the risk of adverse events. For the pain outcome in particular, observed effects were of questionable clinical relevance since the 95% CI did not include the minimal clinically important difference of 0.37 SMDs, which corresponds to 0.9 cm on a 10-cm VAS.

Dailey DL, Vance CGT, Rakel BA, et al. **Transcutaneous Electrical Nerve Stimulation** Reduces Movement-Evoked Pain and Fatigue: A Randomized, Controlled Trial. Arthritis Rheumatol. 2020;72(5):824-836.

Dakin P, DiMartino SJ, Gao H, et al. The Efficacy, **Tolerability, and Joint Safety of Fasinumab** in Osteoarthritis Pain: A Phase IIb/III Double-Blind, Placebo-Controlled, Randomized Clinical Trial. Arthritis Rheumatol. 2019 Jun 17.

Daniels Jane; Gray Richard; Hills Robert K.; et al; on behalf of the LUNA Trial Collaboration. Laparoscopic **Uterosacral Nerve Ablation** (not helfpul) for Alleviating Chronic Pelvic Pain: A Randomized Controlled Trial. JAMA. 2009;302(9):955-961.

Dart RC, Iwanicki JL, Black J, et al. Measuring **Prescription Opioid Misuse** and Its Consequences. Br J Clin Pharmacol. 2021 Feb 19. doi: 10.1111/bcp.14791

Daveluy A, Micallef J, Sanchez-Pena P, et al. Ten-year trend of **opioid and non-opioid analgesic** use in the French adult population. Br J Clin Pharmacol. 2020;10.1111/bcp.14415.

Davis KD, Flor H, Greely HT, et al. **Brain imaging tests for chronic pain**: medical, legal and ethical issues and recommendations. Nat Rev Neurol. 2017 Sep 8.

de Canecaude C, Rousseau V, Chebane L, et al. **Can tramadol really induce hyponatremia**? A pharmacovigilance study. Br J Clin Pharmacol. 2020;10.1111/bcp.14401.

De Gregorio D, McLaughlin RJ, Posa L, et al. **Cannabidiol modulates serotonergic transmission** and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain. Pain. 2019 Jan;160(1):136-150.

de Vos CC, Meier K, Zaalberg PB, et al. **Spinal cord stimulation in patients with painful diabetic neuropathy**: A multicentre randomized clinical trial. Pain. 2014 Aug 29.

Dear BF, Titov N, Perry KN, et al. The **Pain Course**: a randomised controlled trial of a **clinician-guided Internet-delivered cognitive behaviour therapy program** for managing chronic pain and emotional well-being. Pain. 2013 Jun;154(6):942-50.

Dear BF, Gandy M, Karin E, et al. The **Pain Course**: a randomised controlled trial examining an **internet-delivered pain management program** when provided with different levels of clinician support. Pain. 2015 Oct;156(10):1920-35.

Dear BF, Gandy M, Karin E, et al. **The pain course**: a randomised controlled trial comparing a remote-delivered chronic pain management program when provided in online and workbook formats. Pain. 2017 Jul;158(7):1289-1301.

Dear BF, Karin E, Fogliati R, et al. A Cost-effectiveness Analysis of an **Internet-delivered Pain Management Program** Delivered With Different Levels of Clinician Support: Results From a Randomised Controlled Trial. J Pain. 2020 Nov 20:S1526-5900(20)30104-8

Deer TR, Esposito MF, McRoberts WP, et al. A Systematic Literature Review of **Peripheral Nerve Stimulation Therapies** for the Treatment of Pain. Pain Med. 2020 Aug 1;21(8):1590-1603.

Deer TR, Falowski S, Arle JE, et al. A Systematic Literature Review of **Brain Neurostimulation Therapies** for the Treatment of Pain. Pain Med. 2020 Feb 8. pii: pnz371. doi:10.1093/pm/pnz371

Deer TR, Hunter CW, Mehta P, et al. A Systematic Literature Review of **Dorsal Root Ganglion Neurostimulation** for the Treatment of Pain. Pain Med. 2020 Aug 1;21(8):1581-1589.

Degenhardt L, Hungerford P, Nielsen S, et al. **Pharmaceutical Opioid Use Patterns** and Indicators of Extramedical Use and Harm in Adults With Chronic Noncancer Pain, 2012-2018. JAMA Netw Open. 2021 Apr 1;4(4):e213059.

DeGroot H 3rd, Uzunishvili S, Weir R, et al**. Intra-articular injection of hyaluronic acid is <u>not</u>** superior to saline solution injection for ankle arthritis: a randomized, double-blind, placebo-controlled study. J Bone Joint Surg Am. 2012 Jan 4;94(1):2-8.

Demcoe AR, Bohm ER. A 67-year-old woman with **knee pain (osteoarthritis).** CMAJ. 2014 Nov 18;186(17):1311-4.

Deo N, Khan KS, Mak J, et al. Virtual reality for **acute pain in outpatient hysteroscopy**: a randomised controlled trial. BJOG. 2020;10.1111/1471-0528.16377.

Derry CJ, Derry S, Moore RA. **Caffeine** as an analgesic adjuvant for acute pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD009281. DOI: 10.1002/14651858.CD009281.pub2. The addition of caffeine (≥100 mg) to a standard dose of commonly used analgesics provides a small but important increase in the proportion of participants who experience a good level of pain relief.

Derry S, Bell RF, Straube S, et al. **Pregabalin for neuropathic pain** in adults. Cochrane Database Syst Rev. 2019 Jan 23;1:CD007076. Evidence shows efficacy of pregabalin in postherpetic neuralgia, painful diabetic neuralgia, and mixed or unclassified post-traumatic neuropathic pain, and absence of efficacy in HIV neuropathy; evidence of efficacy in central neuropathic pain is inadequate. Some people will derive substantial benefit with pregabalin; more will have moderate benefit, but many will have no benefit or will discontinue treatment.

Derry S, Moore RA. **Topical capsaicin** (low concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2012 Sep 12;9:CD010111. There were insufficient data to draw any conclusions about the efficacy of low-concentration capsaicin cream in the treatment of neuropathic pain.

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. doi: 10.1002/14651858.CD010289.pub2. 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, Wiffen PJ, Moore RA, et al. **Topical lidocaine for neuropathic pain** in adults. Cochrane Database Syst Rev. 2014 Jul 24;7:CD010958. This review found no evidence from good quality randomised controlled studies to support the use of topical lidocaine to treat neuropathic pain, although individual studies indicated that it was effective for relief of pain. Clinical experience also supports efficacy in some patients. Several large ongoing studies, of adequate duration, with clinically useful outcomes should provide more robust conclusions about both efficacy and harm.

Derry S, Wiffen PJ, Hauser W, et al. Oral **nonsteroidal anti-inflammatory drugs for fibromyalgia** in adults. Cochrane Database Syst Rev. 2017 Mar 27;3:CD012332. There is only a modest amount of very low-quality evidence about the use of NSAIDs in fibromyalgia, and that comes from small, largely inadequate studies with potential risk of bias. That bias would normally be to increase the apparent benefits of NSAIDs, but no such benefits were seen. Consequently, NSAIDs cannot be regarded as useful for treating fibromyalgia.

Derry S, Wiffen PJ, Kalso EA, Bell RF, Aldington D, Phillips T, Gaskell H, Moore RA. **Topical analgesics for acute and chronic pain in adults** - an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews 2017, Issue 5. Art.No.: CD008609. There is good evidence that some formulations of topical diclofenac and ketoprofen are useful in acute pain conditions such as sprains or strains, with low (good) NNT values. There is a strong message that the exact formulation used is critically important in acute conditions, and that might also apply to other pain conditions. In chronic musculoskeletal conditions with assessments over 6 to 12 weeks, topical diclofenac and ketoprofen had limited efficacy in hand and knee osteoarthritis, as did topical high-concentration capsaicin in postherpetic neuralgia. Though NNTs were higher, this still indicates that a small proportion of people had good pain relief.

Deshpande A, Mailis-Gagnon A, Zoheiry N, et al. Efficacy and adverse effects of **medical marijuana** for chronic noncancer pain: Systematic review of randomized controlled trials. Can Fam Physician. 2015 Aug;61(8):e372-81.

Deveza LA, Robbins SR, Duong V, et al. Efficacy of a Combination of **Conservative Therapies vs an Education Comparator** on Clinical Outcomes in Thumb Base Osteoarthritis: A Randomized Clinical Trial. JAMA Intern Med. 2021 Mar 8. doi: 10.1001/jamainternmed.2020.7101

Di Martino A, Di Matteo B, Papio T, et al. Platelet-Rich Plasma Versus Hyaluronic Acid Injections for the Treatment of **Knee Osteoarthritis**: Results at 5 Years of a Double-Blind, Randomized Controlled Trial. Am J Sports Med. 2018 Dec 13:363546518814532.

Dowell D, Haegerich TM, Chou R. **CDC guideline for prescribing opioids for chronic pain—United States, 2016**. MMWR Recomm Rep. 2016;65(RR-1): 1-49.

Dowell D, Haegerich TM, Chou R. **CDC guideline for prescribing opioids for chronic pain—United States, 2016**.JAMA. doi:10.1001/jama.2016.1464.

Drug and Therapeutics Bulletin. Management of **medication overuse headache**. BMJ 2010;340:c1305, doi: 10.1136/bmj.c1305 (Published 28 April 2010)

Dubinsky RM, Miyasaki J. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2010 Jan 12;74(2):173-6. Epub 2009 Dec 30. Transcutaneous electric nerve stimulation (**TENS**) is not recommended for the treatment of chronic low back pain (Level A). TENS should be considered in the treatment of **painful diabetic neuropathy** (Level B). Further research into the mechanism of action of TENS is needed, as well as more rigorous studies for determination of efficacy.

Duffy JMN. How should we manage women with unexplained **chronic pelvic pain** in light of uncertainty about the effectiveness of **gabapentin**? BMJ. 2017 Sep 21;358:j3624.

Dulai SK, Firth K, Al-Mansoori K, et al. Does **Topical Anesthetic Reduce Pain During Intraosseous Pin Removal in Children**? A Randomized Controlled Trial. J Pediatr Orthop. 2015 Feb 26.

Duran-Crane A, Laserna A, Lopez-Olivo MA, et al. **Clinical Practice Guidelines and Consensus Statements** About Pain Management in Critically Ill End-of-Life Patients: A Systematic Review. Crit Care Med. 2019 Sep 12.

Düzkaya DS, Bozkurt G, Ulupınar S, et al. The Effect of a **Cartoon and an Information Video** About Intravenous Insertion on Pain and Fear in Children Aged 6 to 12 Years in the Pediatric Emergency Unit: A Randomized Controlled Trial. J Emerg Nurs. 2020 Jul 17:S0099-1767(20)30133-1

Dworkin RH, et al. Pharmacologic management of **neuropathic pain**: evidence-based recommendations. Pain. 2007 Dec 5;132(3):237-51. Epub 2007 Oct 24.

Dykukha I, Malessa R, Essner U, Überall MA. **Nabiximols in Chronic Neuropathic Pain**: A Meta-Analysis of Randomized Placebo-Controlled Trials. Pain Med. 2021 Apr 20;22(4):861-874.

Dziedzic K, Nicholls E, Hill S, et al. **Self-management approaches for osteoarthritis in the hand**: a 2x2 factorial randomised trial. Ann Rheum Dis. 2013 Oct 9.

Eccleston C, Fisher E, Craig L, Duggan GB, Rosser BA, Keogh E. **Psychological therapies** (Internet-delivered) for the management of chronic pain in adults. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD010152. DOI: 10.1002/14651858.CD010152.pub2.

Eccleston C, Hearn L, Williams AC. **Psychological therapies** for the management of chronic neuropathic pain in adults.Cochrane Database Syst Rev. 2015 Oct 29;10:CD011259.
There is insufficient evidence of the efficacy and safety of psychological interventions for chronic neuropathic pain. The two available studies show no benefit of treatment over either waiting list or placebo control groups.

Eggerstedt M, Stenson KM, Ramirez EA, et al. Association of Perioperative Opioid-Sparing Multimodal **Analgesia With Narcotic Use and Pain Control** After Head and Neck Free Flap Reconstruction. JAMA Facial Plast Surg. 2019 Aug 8.

Els C, Jackson TD, Kunyk D, et al. **Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain**: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD012509. A number of adverse events, including serious adverse events, are associated with the medium- and long-term use of opioids for CNCP. The absolute event rate for any adverse event with opioids in trials using a placebo as comparison was 78%, with an absolute event rate of 7.5% for any serious adverse event. Based on the adverse events identified, clinically relevant benefit would need to be clearly demonstrated before long-term use could be considered in people with CNCP in clinical practice. A number of adverse events that we would have expected to occur with opioid use were not reported in the included Cochrane Reviews. Going forward, we recommend more rigorous identification and reporting of all adverse events in randomised controlled trials and systematic reviews on opioid therapy. The absence of data for many adverse events represents a serious limitation of the evidence on opioids. We also recommend extending study follow-up, as a latency of onset may exist for some adverse events.

Emery CF, Olson KL, Bodine A, et al. **Dietary intake** mediates the relationship of body fat to pain. Pain. 2017 Feb;158(2):273-277.

Emir B, Johnson K, Kuhn M, et al. Predictive Modeling of Response to **Pregabalin** for the Treatment of **Neuropathic Pain** Using 6-Week Observational Data: A Spectrum of Modern Analytics Applications. Clin Ther. 2016 Dec 19.

Engquist M, Lofgren H, Oberg B, et al. **Surgery Versus Nonsurgical** Treatment of **Cervical Radiculopathy**: A Prospective, Randomized Study Comparing Surgery Plus Physiotherapy With Physiotherapy Alone With a 2-Year Follow-up. Spine (Phila Pa 1976). 2013 Sep 15;38(20):1715-1722.

Enomoto H, Yasuda H, Nishiyori A, et al. **Duloxetine** in patients with diabetic **peripheral neuropathic pain** in Japan: a randomized, doubleblind, noninferiority comparative study with pregabalin. J Pain Res. 2018 Sep 13;11:1857-1868.

Euppayo T, Punyapornwithaya V, Chomdej S, et al. Effects of **hyaluronic acid combined with anti-inflammatory drugs** compared with hyaluronic acid alone, in clinical trials and experiments in **osteoarthritis**: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2017 Sep 6;18(1):387.

Evaniew N, McCarthy C, Kleinlugtenbelt YV, et al. Vitamin C to Prevent **Complex Regional Pain Syndrome** in Patients With Distal Radius Fractures: A Meta-Analysis of Randomized Controlled Trials. J Orthop Trauma. 2015 Aug;29(8):e235-41.

Evers S, Marziniak M. Clinical features, pathophysiology, and treatment of **medication-overuse headache**. Lancet Neurol. 2010 Apr;9(4):391-401.

Evers S, Jensen R, European Federation of Neurological Societies. Treatment of **medication overuse headache**--guideline of the EFNS headache panel. Eur J Neurol 2011 Sep;18(9):1115-21.

European Medicines Agency (EMA) July/12: equivalent of the US Food and Drug Administration (FDA) yesterday recommended withdrawing **calcitonin nasal spray** — indicated for treating osteoporosis in the European Union — because of an increased risk for **cancer**.

Falk J, Thomas B, Kirkwood J, et al. PEER systematic review of randomized controlled trials: **Management of chronic neuropathic pain** in primary care. Can Fam Physician. 2021 May;67(5):e130-e140.

Fallon M, Walker J, Colvin L, et al. Pain Management in Cancer Center Inpatients: A Cluster Randomized Trial to Evaluate a Systematic Integrated Approach-The Edinburgh Pain Assessment and Management Tool. J Clin Oncol. 2018 May 1;36(13):1284-1290.

Field R, Pourkazemi F, Turton J, Rooney K. **Dietary Interventions** Are Beneficial for Patients with Chronic Pain: A Systematic Review with Meta-Analysis. Pain Med. 2020 Nov 17:pnaa378

Finnerup NB, Attal N, Haroutounian S, et al. **Pharmacotherapy for neuropathic pain** in adults: a systematic review and meta-analysis. Lancet Neurol 2015; online Jan 7.

Filardo G, Di Matteo B, Di Martino A, et al. **Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation**: A Randomized Controlled Trial. Am J Sports Med. 2015 Jul;43(7):1575-82.

Finestone HM, Juurlink DN, Power B, et al. **Opioid prescribing is a surrogate for inadequate pain management resources**. Can Fam Physician. 2016 Jun;62(6):465-8.

Finnerup NB. **Nonnarcotic Methods** of Pain Management. N Engl J Med. 2019 Jun 20;380(25):2440-2448.

Fishbain DA, Pulikal A. Does **Opioid Tapering** in Chronic Pain Patients Result in Improved Pain or Same Pain vs Increased Pain at Taper Completion? A Structured Evidence-Based Systematic Review. Pain Med. 2018 Dec 28.

Fisher E, Eccleston C, Degenhardt L, et al. **Cannabinoids, cannabis, and cannabis-based medicine** for pain management: a protocol for an overview of systematic reviews and a systematic review of randomised controlled trials. Pain Rep. 2019 Apr 30;4(3):e741.

Fournier J-P, Azoulay L, Yin H, et al. **Tramadol use and the risk of hospitalization for hypoglycemia** in patients with noncancer pain [online December 8, 2014]. JAMA Intern Med. doi:10.1001 /jamainternmed.2014.6512.

Franco JV, Turk T, Jung JH, et al. **Non-pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome**. Cochrane Database Syst Rev. 2018 Jan 26;1:CD012551.
Some of the interventions can decrease prostatitis symptoms in an appreciable number without a greater incidence of adverse events. The QoE was mostly low.

Fowler M, Ali S, Gouin S, et al. Knowledge, attitudes and practices of Canadian **pediatric emergency physicians regarding short-term opioid use**: a descriptive, cross-sectional survey. CMAJ Open. 2020 Mar 16;8(1):E148-E155

Franklin GM. **Opioids for chronic noncancer pain**: A position paper of the American Academy of Neurology (**AAN**) . Neurology. 2014 Sep 30;83(14):1277-84.

Fransen M, McConnell S, Harmer AR, et al. Exercise for **osteoarthritis of the knee**. Cochrane Database of Systematic Reviews 2015, Issue 1. Art. No.: CD004376. DOI: 10.1002/14651858.CD004376.pub3. High-quality evidence indicates that land-based therapeutic exercise provides short-term benefit that is sustained for at least two to six months after cessation of formal treatment in terms of reduced knee pain, and moderate-quality evidence shows improvement in physical function among people with knee OA. The magnitude of the treatment effect would be considered moderate (immediate) to small (two to six months) but comparable with estimates reported for non-steroidal anti-inflammatory drugs. Confidence intervals around demonstrated pooled results for pain reduction and improvement in physical function do not exclude a minimal clinically important treatment effect. Since the participants in most trials were aware of their treatment, this may have contributed to their improvement. Despite the lack of blinding we did not downgrade the quality of evidence for risk of performance or detection bias. This reflects our belief that further research in this area is unlikely to change the findings of our review.

Freo U, Romualdi P, Kress HG. T**apentadol for neuropathic pain**: a review of clinical studies. J Pain Res. 2019 May 16;12:1537-1551. doi: 10.2147/JPR.S190162.eCollection 2019.

Freynhagen R, Bennett MI. Diagnosis and management of **neuropathic pain**. BMJ. 2009 Aug 12;339:b3002. doi: 10.1136/bmj.b3002.

Friesen LN, Hadjistavropoulos HD, Schneider LH, et al. Examination of an **Internet-Delivered Cognitive Behavioural Pain Management** Course for Adults with **Fibromyalgia**: A Randomized Controlled Trial. Pain. 2016 Dec 15.

Frost DA, Soric MM, Kaiser R, Neugebauer RE. Efficacy of **Tramadol for Pain Management** in Patients Receiving Strong Cytochrome P450 2D6 Inhibitors. Pharmacotherapy. 2019 Jun;39(6):724-729.

Fukushima FB, Bezerra DM, Villas Boas PJ, Valle AP, Vidal EI. **Complex regional pain syndrome**. BMJ. 2014 Jun 25;348:g3683.

Furyk J, Levas D, Close B, et al. **Intravenous versus oral paracetamol (acetaminophen)** for acute pain in adults in the emergency department setting: a prospective, double-blind, double-dummy, randomised controlled trial. Emerg Med J. 2018 Mar;35(3):179-184.

Furuno JP, Noble BN, Fromme EK, et al. **Decreasing Trends in Opioid Prescribing** on Discharge to Hospice Care. J Pain Symptom Manage. 2021 Apr 10:S0885-3924(21)00279-7.

Gadkaree SK, Shaye DA, Occhiogrosso J, Lee LN. Association Between **Pain and Patient Satisfaction After Rhinoplasty**. JAMA Facial Plast Surg. 2019 Sep 19.

Gallagher HC, Gallagher RM, Butler M, et al. **Venlafaxine for neuropathic pain** in adults. Cochrane Database Syst Rev. 2015 Aug 23;8:CD011091. We found little compelling evidence to support the use of venlafaxine in neuropathic pain. While there was some third-tier evidence of benefit, this arose from studies that had methodological limitations and considerable risk of bias. Placebo effects were notably strong in several studies. Given that effective drug treatments for neuropathic pain are in current use, there is no evidence to revise prescribing guidelines to promote the use of venlafaxine in neuropathic pain. Although venlafaxine was generally reasonably well tolerated, there was some evidence that it can precipitate fatigue, somnolence, nausea, and dizziness in a minority of people.

Garland EL, Baker AK, Larsen P, et al. Randomized Controlled Trial of **Brief Mindfulness Training** and Hypnotic Suggestion for Acute Pain Relief in the Hospital Setting. J Gen Intern Med. 2017 Jul 12.

Garland EL, Brintz CE, Hanley AW, et al. **Mind-Body Therapies** for Opioid-Treated Pain: A Systematic Review and Meta-analysis. JAMA Intern Med. 2019 Nov 4. doi:10.1001/jamainternmed.2019.4917.

Gaskell H, Moore RA, Derry S, Stannard C. **Oxycodone for neuropathic pain and fibromyalgia** in adults. Cochrane Database Syst Rev. 2014 Jun 23;6:CD010692. No convincing, unbiased evidence suggests that oxycodone (as oxycodone CR) is of value in treating people with painful diabetic neuropathy or postherpetic neuralgia. There is no evidence at all for other neuropathic pain conditions, or for fibromyalgia. Adverse events typical of opioids appear to be common.

Gibson W, Wand BM, Meads C, et al. Transcutaneous electrical nerve stimulation (**TENS) for chronic pain** - an overview of Cochrane Reviews. Cochrane Database Syst Rev. 2019 Feb 19;2:CD011890. We found the methodological quality of the reviews was good, but quality of the evidence within them was very low. We were therefore unable to conclude with any confidence that, in people with chronic pain, TENS is harmful, or beneficial for pain control, disability, health-related quality of life, use of pain relieving medicines, or global impression of change.

Gilron I, et al. **Neuropathic pain**: a practical guide for the clinician. CMAJ. 2006 Aug 1;175(3):265-75.

Gilron I, Bailey JM, Tu D, et al. **Nortriptyline and gabapentin**, alone and in combination for **neuropathic** pain: a double-blind, randomised controlled crossover trial. Lancet. 2009 Oct 10;374(9697):1252-61. Epub 2009 Sep 30.

Gilron I, Jensen TS, Dickenson AH. **Combination pharmacotherapy** for management of **chronic pain**: from bench to bedside. Lancet Neurol. 2013 Sep 24.

Gilron I, Chaparro LE, Tu D, et al. Combination of **pregabalin with duloxetine for fibromyalgia**: a randomized controlled trial. Pain. 2016 Jul;157(7):1532-40.

Glare P, Aubrey KR, Myles PS. **Transition from acute to chronic pain after surgery**. Lancet. 2019 Apr 13;393(10180):1537-1546

Goebel A, Bisla J, Carganillo R, et al. Low-dose intravenous **immunoglobulin treatment for long-standing complex regional pain syndrome**. A randomized trial. Ann Intern Med. 2017;167:476-83.

Gohir SA, Eek F, Kelly A, et al. Effectiveness of Internet-Based **Exercises Aimed at Treating Knee Osteoarthritis**: The iBEAT-OA Randomized Clinical Trial. JAMA Netw Open. 2021 Feb 1;4(2):e210012

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Rows A-F: *Generally, trials **compared to placebo** (± background treatment); however, some small head-to-head trials. Most trials **≤ 12 weeks duration** (exceptions noted below). Typically, we reported the following outcomes: ≥ 30-50% reduction in pain, change in pain (based on a pain scale e.g. NRS, VAS), global improvement, or change in function.*

A: Low Back Pain (LBP), Chronic [4] ACP'17,5 NICE'16,6,7

I	Non-drug tx: may include: **exercise** (**NNT=4-8**) reduced pain & less recurrance[8], ("staying active" or "activity as tolerated" if acute LBP), physio, multidisciplinary rehab, tai chi, yoga, Pilates[256], stress reduction, mindfulness (appears equivalent to CBT),[9] CBT, combined chiropractic care (improved short-medium term pain in acute-subacute LBP)[259], acupuncture (limited evidence,uncertain effect in chronic)[258], massage (limited short-term benefit pain +/- function, patient satisfaction)[257]. Medi-Taping – appeared beneficial (treating pelvic obliquity with a combination of manual treatment of trigger points and kinesio taping)[262] Acupuncture: possible/unclear benefit. (? Benefit compared: a) to placebo NNT=6, b) to sham acupuncture NNT=20; c) benefit lost completely if limited to higher quality, longer duration RCTs.) {Acute LBP: consider heat.}
II	Acetaminophen: *does not appear effective and is not recommended by guidelines [ACP'17, NICE'16]; however, may be trialed as relatively safe compared to alternatives.* Acute: 1 RCT (n=1652), 4g/day had similar effects vs placebo for pain & disability.[10] No difference between acetaminophen and NSAIDs (4 RCTs, n=309).[11] Chronic: not adequately studied vs placebo e.g. 1 RCT (n=133) studied 2 days of therapy; however, 1 small RCT (n=30) showed no significant difference between acetaminophen 4g/day vs an NSAID. Not studied in subacute LBP.[12,13]
III	Oral NSAIDs: *appear effective for acute & chronic low back pain.[ACP'17, NICE'16] COXIB and non-selective NSAIDs appear to have similar benefit, but limited head-to-head studies.* Acute: meta-analysis (N=4, n=745), NSAIDs x ≤1 week ↓ mean pain score (~8 on 0-100 VAS) and ↑ global improvement (RR. 1.2) vs placebo; but also increased AE (RR 1.25). Head to head studies: similar effect between NSAIDs vs acetaminophen (N=4, n=309); limited RCT data vs muscle relaxants or weak opioids (i.e. codeine) but appear similar. The majority of RCTs report no difference between types of NSAIDs.[10] Chronic: meta-analysis (N=6, n=1354), NSAID ↓ mean pain score (~7 on 0-100 VAS) and improved disability vs placebo; however, when limited to high quality studies differences were NS. Head to head studies: in 1 RCT (n=30), NSAID vs acetaminophen 4g/day demonstrated similar effects. In 2 RCTs (n=1598), celecoxib 400mg/day ↓ pain (**NNT~10**) and ↓ AE vs tramadol 200mg/day. In 3 RCTs (n=530) similar effect among NSAIDs.[12] Topical NSAIDs: *limited data; however, may consider if localized pain.*
IV	Duloxetine: *may be effective in chronic low back pain (including non-neuropathic low back pain).[ACP'17] May consider TCAs e.g. if neuropathic component to low back pain.* Chronic: in RCTs (largest study, n=404), duloxetine 60-120mg/d generally ↓ mean pain score, but inconsistent results for ≥30% reduction in pain; ↑ discontinuation due to AE (**NNH~6-12**) & ↑ AE (especially nausea, dry mouth, and somnolence).[14,15,16] ✓Health CND indication- chronic low back pain. (?Low dose amitriptyline 25mg - vs active control with benztropine: less disability at 3 mo but not 6.[260]) (TCAs & SNRIs may be effective in sciatica very low quality evidence.[244]) Venlafaxine: no RCTS in low back pain available. One systematic review (2020) found that impact of SNRIs on pain/disability is small & of questionable clinical importance moderate certainty .[244]
V	Gabapentinoids: *may consider if neuropathic component to LBP. Otherwise, limited data, of little to no benefit, and not generally recommended.* [ACP'17, NICE'16] There was no difference between gabapentin 300-3600mg/d vs placebo in a meta-analysis (N=3, n=185). Pregabalin ≤600mg/d was inferior to active treatment (amitriptyline ~50mg/d, celecoxib~200-400mg/d, **TRAMACET** 2 tabs/d) for pain reduction in a meta-analysis (N=3, n=332); also, increased risk of harms, especially dizziness **NNH=7-11**.[17] In addition, 1 RCT (n=209) showed similar leg pain associated with sciatica results in those receiving pregabalin or placebo but ↑ AE with pregabalin (especially dizziness).[18] Gabapentinoids may be of potential benefit if neuropathic component to LBP or possibly if radicular pain (i.e. pain radiating from the spine to a limb).[16]
VI	Opioids: *not generally recommended.* [ACP'17, NICE'16] *May consider during an acute exacerbation or when other therapies ineffective. Consider guideline recommendations for safe use.* Tramadol: in chronic LBP, tramadol 150-300mg/day ± acetaminophen ↓ pain and disability vs placebo in a systematic review (N=5 RCTs, n=1378).[19] However, in 2 RCTs (n=1598) there was ↓ pain (**NNT~10**) and & ↓ AE with celecoxib 400mg/day vs tramadol 200mg/day.[20] Buprenorphine: in chronic LBP, transdermal buprenorphine ~20mcg/h ↓ pain but not disability (meta-analysis N=2, n=653).[18] Strong opioids: role is unclear. In chronic LBP, strong opioids (overall mean dose studied ~110MED/d; range 40-243 MED/d) ↓ pain & disability (meta-analysis N=6, n=1887); however, other reviews suggest no clinically important pain relief or improvement in disability with opioids. Also, increased risk of AEs **NNH~9-17** (e.g. somnolence, nausea, constipation).[18,21,22]
VII	Cannabinoids: no RCTs in LBP available.
VIII	Muscle relaxants (non-benzodiazepine): *may consider as a potential short term option (≤2 weeks) in acute LBP.* ↓ pain/muscle spasm. Cyclobenzaprine **NNT=3** at 10 days (no difference between 5mg vs 10mg)[240]; however, ↑ AE **NNH=12** (esp CNS **NNH=9**) and no significant difference >2 weeks. Most data with cyclobenzaprine, tizanidine, or baclofen.[23] Interventional procedures: *may have value especially in difficult to treat patients* (e.g. facet joint injections, medial branch blocks & neurotomy, sacroiliac joint injections & neurotomy, interlaminar & transforaminal epidural steroid injections, intradiscal glucocorticoid injection). {Ketamine +/- magnesium infusions: evidence mixed; may not be effective in refractory cases; harm may outweigh benefit.[246]}

B: Osteoarthritis (OA)

I	Non-drug treatment: surgery (hip, knee), if severe. Tailored exercise therapy improved knee OA at 3 months in those with comorbidities.[24] Internet based options effective.[243] Low intensity training better than high intensity for knee OA.[242] Consider: weight loss, physiotherapy, tai chi, CBT.[248] Braces, splints, orthotics, & assistive devices helpful e.g. heat, cold.
II	Acetaminophen: *appears to offer little clinically meaningful benefit, but trial often recommended for older adults as considered relatively safe compared to alternatives.* [232] For OA knee/hip: meta-analysis (N=10, n=2541), acetaminophen ~3-4g/day vs placebo reached a statistically but not clinically significant ↓ pain and function; studies were typically 6-12 weeks in duration, except 1 study which was 6 months.[25,26] For OA knee/hip: meta-analysis (N=15, n=2991), acetaminophen 2.6-4g/day vs NSAIDs (e.g. ibuprofen 1200-2400mg/d, diclofenac 150mg/d, celecoxib 200mg/d, naproxen 440-750mg/d) resulted in a small ↓ pain in favour of NSAIDs (Mean Difference= -0.29, 95% CI -0.35 to -0.22); study duration range was 1-104 wks (median duration not reported).[27]
III	Topical NSAIDs: *appear effective for single joint osteoarthritis; limited data vs oral NSAIDs.* Meta-analysis (N=39, n=10,631), in OA (typically knee) topical NSAID ↓ pain **NNT=7-10** vs topical placebo; study duration was ~6-12 weeks; most studies assessed **VOLTAREN EMULGEL** (1-3%) or topical ketoprofen. Limited data; however, topical & oral NSAIDs appeared similar.[28, 238] Oral NSAIDs: *appear effective; potentially greater pain reduction than acetaminophen but similar effects as opioids. COXIB and non-selective NSAIDs appear to have similar benefit, but limited head-to-head studies.* For OA knee/hip: meta-analysis (N=15, n=2991), acetaminophen 2.6-4g/day vs NSAIDs (e.g. ibuprofen 1200-2400mg/day, diclofenac 150mg/day, celecoxib 200mg/day, naproxen 440-750mg/day) resulted in a small pain reduction in favour of NSAIDs (Mean Difference= -0.29, 95% CI -0.35 to -0.22); study duration range 1-104 weeks (median duration not reported).[26] No agent clearly superior (indirect comparisons).[29,30,31]
IV	Duloxetine: *may be effective for knee OA.* Meta-analysis (N=3, n=1011), 60-120mg/d vs placebo ↓ knee pain **NNT~6**; however, ↑ risk of discontinuation due to AEs (esp nausea, constipation, diarrhea, dizziness, somnolence, and insomnia).[225, 227] ✓(Health CND indication- OA of the knee)
V	Gabapentinoids: *limited data; not generally recommended.* One RCT (n=89) in knee OA demonstrated similar results for pain and function among those treated with pregabalin 25mg HS or meloxicam 10mg/d; however combination therapy (pregabalin + meloxicam) was statistically more effective than monotherapy.[32] Another study in hand OA (n=65) showed ↓ pain vs placebo.[Sofat'17]
VI	Opioids: *appear to have some benefit; consider use during an acute exacerbation or when other therapies are ineffective.* Tramadol: meta-analysis, tramadol 150-250mg/d vs placebo ↓ pain score (~9 on 0-100 scale) and resulted in global improvement (**NNT=6**); however, ↑ major AE (**NNH=8**). Variable results vs active comparators.[33,34] Tapentadol: small benefit vs placebo (**NNT=16** after 12 wks; **NNH=10**).[35] Strong opioids: meta-analysis, opioids vs placebo resulted in a ↓ pain (**NNT=10**) & ↑ in function (**NNT=12**), but ↑ withdrawal due to AE (**NNH=21**) & ↑ any AE (**NNH=14**); median dose 59 MED/d (range 13-160 MED/d) & no association between daily equivalent dose & improvement in pain or function; median treatment duration 4 wks (range 3 days to 6 months).[36] Elderly: AEs ↑.[Megale 18]
VII	Cannabinoids: no RCTs in osteoarthritis available.[37]
VIII	Other: Intraarticular glucocorticoid injections for knee OA may result in short-term pain relief, data for longer-term outcomes are less favourable.[38,39] (Intra-articular triamcinolone vs saline, to symptomatic knee every 12 weeks, resulted in greater cartilage volume loss and no difference in pain over 2 yrs.)[40] Tanezumab subcutaneous q8-wks for OA of hip or knee was effective.[235] Hyaluronic acid injection (HA) (viscosupplementation): some evidence supports a role in knee OA, but overall evidence is conflicting. May consider after failure of other treatment.[41] Platelet-rich-plasma, OA-Knee ?more effective than HA.[230] Combos: limited data; some combos studied include acetaminophen, NSAID, tramadol.[42,33] Glucosamine, chondroitin, or both: likely not effective for pain or function,[43,44,45] however some systematic reviews that include smaller studies of lower quality find some effect (glucosamine 1500mg/day: NNT = 11 over 4-156 weeks; chondroitin 800-1200mg/day NNT=9 over 12-48 weeks; however metanalysis rerun by PEER found likely ineffective)[261]. Topicals, counter-irritants (e.g. capsaicin 0.025%): [46,47,48] may provide some benefit. Bisphosphonates in **females** with knee OA needed knee replacement surgery **less often** in a retrospective study (n=4012) compared to no bisphosphonate therapy.[AnnRheumDis2017] Emerging: stem cell injections for OA; preliminarily +'ve but bias & low level of evidence.[49]

C: Neuropathic Pain [50] CPS'16, [51] NICE'13(updated'17),[52], PEER Simplified Guidelines/SR 2021 (N=67), [265a/b] **PDN**=painful diabetic neuropathy **PHN**=post-herpetic neuralgia

I	Non-drug treatment: a multifactorial approach (physiotherapy, exercise, psychological treatment) is essential.[CPS'14] Other: e.g. radiofrequency ablation, spinal cord stimulation [10-kHz]
II, III	Acetaminophen & NSAIDS: *generally not recommended; however may use during an acute exacerbation.* [Expert Opinion] No RCTs in neuropathic pain available.[51]
IV	TCAs & SNRIs: *appear effective;* [CPS'14(1st line)] *amitriptyline (potentially nortriptyline) & duloxetine may be preferred.* [NICE'13(updated'17; 1st line, Strong Recommendation)]*; quality of evidence limited for TCAs* TCAs: [CPS'14(1st line)] meta analysis (N=15, n=948), PDN, PHN: ↓ pain **NNT=4** but benefit <u>may be overestimated</u> as based on poor quality trials; ↑withdrawal due to AE **NNH=12-14** vs placebo; majority of studies included amitriptyline [NICE'13 updated'17; 1st line, Strong Recommendation] (average dose 25-100mg/d, range 10-200mg/d) but nortriptyline (25-100mg/d), desipramine, & imipramine also studied.[51,53,54,55,56] Limited data; however, head-to-head studies suggest similar benefit among TCAs, and nortriptyline may be better tolerated.[57,58] One RCT (n=83) reported similar benefit among amitriptyline 50-75mg/d, duloxetine 60-120mg/d, & pregabalin 300-600mg/d.[59] SNRIs: [CPS'14(1st line)] duloxetine [NICE'13(updated'17; 1st line, Strong Recommendation)] meta-analysis (N=8, n=2718), PDN: duloxetine 40-120mg/d, **NNT=6** for decreased pain; but ↑withdrawal due to AE (**NNH=10** at 120mg/d and **NNH=20** at 60mg/d). Adverse effects included nausea, dry mouth, dizziness & somnolence vs placebo (generally ≤30mg/d was NS). Harms appear greater with 120mg/d vs 60mg/d, but not benefits.[51,60] ✓(Health CND indication- PDN). One study (n=83) RCT reported similar benefit among duloxetine 60-120mg/d, amitriptyline 50-75mg/d, & pregabalin 300-600mg/d.[58] In addition, duloxetine 60mg/d was shown to be non-inferior to pregabalin 300mg/d in one RCT (N=407) and superior in an exploratory analysis of another RCT (N=804).[61] May consider venlafaxine 150-225mg/d or desvenlafaxine 200-400mg/d; however, less data & less robust (e.g. small sample size) vs duloxetine.[51,62] **PEER:** Duloxetine – most evidence (or venlafaxine), over 6-13 wks: **NNT=6-8**; **NNH=13**.[265] Subgroup analysis found benefit at more than 12 weeks (but not less).
V	Gabapentin & pregabalin: *appear effective.* [CPS'14 (1st line), NICE'13(updated'17; 1st line, Strong Recommendation), PEER 2021] Gabapentin: **PEER** (over 2-16 wks): **NNT=6**; **NNH=22.**[265] Meta-analysis (N=37 RCTs, n=5914), gabapentin 900-2400-3600mg/d vs placebo; **<u>PHN</u>**: ↓ pain **NNT~7** & ↑global response **NNT~10**; **<u>PDN</u>**: ↓ pain **NNT=6-10** & ↑global response **NNT=5-10**; but ↑D/C due to AE **NNH=30**, ↑AE (dizziness, ataxia/gait disturbance, somnolence, peripheral edema) **NNH=8-20**. SAE=NS.[63] No clear dose-response. In 2 RCTs (n≤75), gabapentin (1500-2700mg/d) had a similar effect on pain and less AEs vs TCAs (nortriptyline 75mg/d,[64] amitriptyline 50-75mg/d).[65] Pregabalin: **PEER** (over 5-15 wks): **NNT=7**; **NNH=17.**[265] Meta-analysis (N=45, n=11906), pregabalin 300-600mg BID vs placebo in **<u>PHN:</u>** ↓ pain >50% **NNT=4-5**, ↑global response **NNT=5-6**, DC due to AE: **NNH=7-11**; **<u>PDN</u>**: ↓ pain >50% **NNT=8-14 ,** ↑D/C due to AE **NNH=12-35**, ↑ any AE **NNH=8-11** e.g. dizziness, somnolence as well as peripheral edema. Potentially greater response (NNT=6), but also ↑AE, with 600mg/d vs lower doses for some patients (mixed evidence).[51,66,233] ✓(Health CND indication- PDN, PHN, SCI). One RCT (n=83) reported similar benefit among pregabalin 300-600mg/d, duloxetine 60-120mg/d, amitriptyline 50-75mg/d.[58] In addition, duloxetine 60mg/d was shown to be non-inferior to pregabalin 300mg/d in 1 RCT (N=407) and superior in an exploratory analysis of another RCT (N=804).[60] Combining a gabapentinoid (e.g. gabapentin) with a TCA (e.g. nortriptyline) or an opioid (e.g. morphine) in neuropathic pain may be more efficacious than either drug alone; however, overlapping AE profiles including CNS AEs may adversely affect function.[67,68]
VI	Tramadol: *may consider during an acute exacerbation* [NICE'13(updated'17, Weak Recommendation)] *or when other therapies are ineffective*[CPS'14(2nd line;)]*; watch DIs (5HT & seizure risk).* Meta-analysis (N=6, n=438), 300-400mg/day vs placebo ↓ pain **NNT=5**, but ↑D/C due to AE **NNH=9**, ↑AE **NNH~5** (dizziness, fatigue, dry mouth, constipation, nausea).[51,69] Tapentadol: limited RCTs with mixed results.[51] Buprenorphine: lacks RCTs.[70] Strong opioids: *role is unclear; may consider during an acute exacerbation or when other therapies are ineffective.* [CPS'14(2nd line), NICE'13(updated'17; avoid unless under specialty care, Weak Recommendation), PEER 2021] **PEER: NNT=10**, **NNH=12** "Benefits may not exceed harms."[265] Meta-analysis, morphine & oxycodone vs placebo ↓ pain **NNT=5**; however, inconsistent results among individual trials (e.g., 4/8 trials were beneficial [mean dose: 45-91 MED/d; max dose: 90-240 MED/d], 4/8 trials were neutral [max dose: 15-180 MED/d]) and ↑D/C due to AE **NNH=12**.[51,71,72] Majority of data with a positive outcome was with MED/d ≤90. Other opioids: inconclusive as limited data based on recent Cochrane systematic reviews: methadone (N=3, n=105) dose range studied: 10-80mg/d;[73] fentanyl (N=1, n=258) dose range studied: 12.5-50mcg/h;[74] hydromorphone (N=1, n=117) dose range studied: 12-64mg/d.[75]
VII	Cannabinoids: *role unclear.* [CPS'14(3rd line), NICE'13(updated'17; avoid unless under specialty care, Weak Recommendation)] Inconclusive evidence. In general, studies for cannabinoids are short, with few patients enrolled, and are inadequately blinded. One systematic review suggested cannabinoids may decrease chronic neuropathic pain (**NNT=11**),[76] although other systemic reviews have found largely negative results.[51] Adverse effects are common, e.g. feeling 'high' **NNH=4**; sedation **NNH=5**; speech disorders **NNH=5**; dizziness **NNH=5**; and ataxia/muscle twitching **NNH=6**. ✓ **SATIVEX** THC:CBD buccal spray has a Health Canada indication for adjunctive tx in multiple sclerosis neuropathic pain or spasticity. The vast majority of evidence in pain is for **THC**, **THC-analogues**, or **THC-containing formulations**;[76] CBD alone largely unstudied; may be inferior.[77] A metaanalysis for nabiximols found that it was superior to placebo (small effect size) in reducing neuropathic pain.[269]
VIII	Carbamazepine: *1st line **trigeminal neuralgia;***[CPS'14] Other: lamotrigine, gabapentin, botox, pregabalin, phenytoin.[236] Topiramate: **PEER** (over 12wks; limited evidence) similar efficacy to gabapentinoids (**NNT=8**), but more harm leading to discontinuation (**NNH=7**).[265] Topical: Lidocaine 2nd line for localized PHN[CPS'14]; most studies with lidocaine patch[USA, not CND]. [78,79,80,249] May be useful in superficial neuropathic pain (lidocaine [**XYLOCAINE** 5% Ointment, **MAXILENE** 4 & 5% Cream], & capsaicin [Cream]).[81] Capsaicin Crm 0.075%: **PEER NNT 10**; **NNH=25** [265]; (higher strength better than lower, but may start with lower for tolerability). {Capsaicin 8% Patch also effective [USA only]}. Compounded options usually in penetration-enhancing vehicles. May consider nitrate spray (apply to legs or bottom of feet HS) in PDN.[ADA'13] Botulinum toxin A: 4th line.[CPS'14] Combo pharmacotherapy*: if partial, but inadequate pain relief with monotherapy may consider combinations of 1st and 2nd line agents.* [CPS'14] The following regimens have variable effect on pain/function & typically ↑AEs; but may allow for lower doses: gabapentinoid + TCA; gabapentinoid + duloxetine; opioid + gabapentinoid (caution ↑ opioid related death), or TCA or duloxetine (average opioid dose 15-60 MED/day, max 120 MED/day).[51,82,83] *DiabaSens* Cream is a "blend of ingredients" [L-arginine, L-citrulline, Cinnamomum zeylanicum] natural health product with <u>no evidence for benefit</u>.[237]

D: Fibromyalgia[84 EULAR'17,85 CDN'12,86] (e.g. chronic widespread pain, central sensitized pain syndrome)

I	Non-drug treatment: patient education of diagnosis, treatment, expectations, credible info sources. Physical exercise[CND CNCP'17(moderate), EULAR'17(Ia,strong)] (moderate intensity 20-30min, 2-3d/wk): meta-analysis (N=13 RCTs, n=839), ↓ pain **NNT=4**, ↑ function **NNT=6**, & fatigue; studied up to ~4 years (persistent effects for pain).[87] Consider giving patient an exercise prescription. Physiotherapy (i.e. electric stimulation, acupuncture, whole-body vibration, massage, resistance training, acupoint stimulation, aquatic physical therapy) ↓ pain ±↑ function.[88] Also consider sleep hygiene, CBT[245], and self-management support (e.g. emotional awareness & expression therapy [226]). Acupuncture: one systematic review (12 RCTs) found on average a 1/10 point reduction in pain immediately after treatment (moderate quality evidence).[89] An early, 3wk spa treatment appeared effective.[255]
II	Acetaminophen: *generally not recommended; however, may be useful in some patients.* [CDN'12(Expert Opinion)] No RCTs of acetaminophen monotherapy in fibromyalgia available. (**see D-VIII** for **TRAMACET**).
III	NSAIDs: *generally not recommended;*[EULAR'17(weak)] *however, may consider if comorbid pain disorder (e.g. OA).*[CDN'12(expert)] Meta-analysis (N=6 RCTs, n=292), NSAIDs (e.g. ibuprofen 2400mg/d, naproxen 1000mg/d) did not reduce pain compared to placebo.[90]
IV	TCAs & SNRIs: *may be used;*[CDN'12(1A)] *amitriptyline (potentially nortriptyline) or duloxetine may be preferred.*[EULAR'17(Ia,weak)] Amitriptyline: meta-analysis (N=9, n=649), 25-50mg/d vs placebo ↓ pain **NNT=4**, effect on other outcomes (e.g. function, QOL, mood, fatigue) either limited ± conflicting; withdrawal due to AEs were no different compared to placebo (RR 1, 95% CI 0.5 to 2.2), but ↑AEs **NNH=4** (especially: dry mouth, fatigue, drowsiness, somnolence); studied up to 6 months.[52,91] Nortriptyline: limited data, RCT (n=188) ↑ function & global improvement vs baseline (pain score not recorded), similar to amitriptyline.[92] Duloxetine: meta-analysis (N=6, n=2,249), 60-120mg/day ↓ pain **NNT~8**; 30mg/d was NS (RR 1.01 95% CI 0.75 to 1.35); improved global effect (change of ~3.5/10 vs baseline; absolute difference -0.5 ?clinical significance); ↑SF-35 mental score (all doses); but ↑ withdrawals due to AE (dose-dependent) **NNHaddedremoved =9** (120mg/d), **NNH=18** (60mg/d) & ↑AE (all doses) **NNH~9** (esp nausea, dry mouth, dizziness, somnolence); studied up to 6 mos.[59] ✓(Health CND indication) One disadvantage of SNRIs in fibromyalgia: a beneficial effect on sleep is lacking. Venlafaxine: limited data, no RCTs; however, may provide possible benefit.[93] {Another SNRI, milnacipran, may have similar benefit/harm as duloxetine.} SSRIs: *may consider; however, role is unclear.*[CDN'12(1A), EULAR'17 (weak recommendation against)] Meta-analysis (N=7, n=383), which included citalopram, fluoxetine, paroxetine ↓ pain **NNT=10** (however, 95% CI 5-100), ↑ global improvement **NNT=7**, ↓ depression **NNT=13**; withdrawal due to AE similar to placebo.[94] Mirtazapine: recent (2016) RCT (n=430), 30mg/d ↓ pain **NNT=7**, ↑ function; but ↑AE **NNH=9** (including somnolence, ↑LFTs, ↑ weight [~2kg]).[95]
V	Pregabalin: *appears effective and may be a preferred option.*[EULAR'17(Ia,weak)] Meta-analysis (N=8 RCTs, n=4147), pregabalin 300-600mg/day vs placebo ↓ pain **NNT~10** and improved global impression **NNT~12**; 150mg/d was NS. ?improvements in fatigue and anxiety/depression. Dose-related ↑ AE with >150mg/d (e.g. withdrawals due to adverse effects **NNH=6-17**; any adverse effect **NNH=6-9**; weight gain **NNH=8**); all doses: ↑ dizziness, somnolence, peripheral edema **NNH=4-19**.[96] Efficacy and safety data up to 1 year.[97] If ↑ daytime adverse effects, consider dosing only at bedtime as 1 RCT (n=177) reported similar benefit and possibly less adverse effects vs BID dosing.[98] ✓ (Health Canada indication) Gabapentin: *limited data*.[99] RCT (n=150), gabapentin 1,800mg/d (1,200 - 2,400mg/d) ↓ pain **NNT=5**, ↑global improvement **NNT=4**; but ~2x ↑D/C due to AE & ↑AE **NNH=5-13** for dizziness, sedation, lightheadedness, weight gain.[100]
VI	Tramadol: *may consider during an acute exacerbation or when other therapies are ineffective.* [CDN'12(D), EULAR'17(Ib,weak)] In one RCT (n=69), tramadol ~200-300mg/d vs placebo ↓ pain **NNT=4**, but no difference in function (p=0.371); AE similar, but run-in period prior.[101,102,103] Strong Opioids: *use is discouraged.* [EULAR'17(strong) CDN'12(D)] No RCTs of strong opioids (e.g. oxycodone) in fibromyalgia available[104] and prospective observational data suggests worse pain & function outcomes vs non-opioid therapy; also, risk of harms.[105,106,107,108]
VII	Cannabinoids: *limited data*. Nabilone 0.5-2mg had conflicting effects on pain and function in 2 RCTs (both studies had <50 subjects), but ↑AE (e.g. 1.5x) vs comparator.[109,110,111]
VIII	Cyclobenzaprine (TCA-like): *may consider;* [EULAR'17(Ia,weak)] *however, limit to short-term use.* Meta-analysis (N=5 RCTs, n=312), 10-40mg/d divided BID-TID ↓ pain ~35% vs baseline @4wks, no difference >4wks; ↑ patient rated global improvement **NNT=5** over 1-3 months.[112] **NNH=4**.[113] Naltrexone (4.5mg/d[not commercially available; 50mg scored tablet available CDN]): RCT (n=31), may ↓pain and improve general satisfaction in women, but ↑headache & vivid dreams (**NNH=5-8**).[114] Combo pharmacotherapy: *may be required,*[CDN'12(D] *but limited data; consider following regimens* (variable effect of pain/function and typically ↑AEs): -SNRI/SSRI am + pregabalin HS or divided BID: e.g. duloxetine (average dose 100mg/d) + pregabalin (average dose 380mg/d)[115] or paroxetine 25mg am + pregabalin 75mg HS[116] -SNRI/SSRI am + TCA HS: e.g. fluoxetine 20mg am + amitriptyline 25mg HS[117] -TRAMACET 325/37.5mg 1-2 tabs QID (average 4 tablets/day)[118]

E: Other Pain, Chronic

I	1) Physical and exercise therapy: "11 evidence-based guidelines included recommendations about the use of physical therapy interventions for the management of chronic, non-cancer pain. Overall, guidelines supported the use of physical & exercise therapy, manual therapy (i.e. spinal manipulation therapy & mobilization techniques), acupuncture, massage, & yoga. However, guidelines were typically limited with respect to the optimal frequency and duration of treatment & sometimes provided contradictory recommendations."[119] 2) Behavioural and psychological interventions: "CBT was recommended across all guidelines. Hypnosis, relaxation, biofeedback and mindfulness were also recommended in several guidelines."[120] (Some online availability for mindfulness & CBT training, e.g. https://onlinetherapyuser.ca). Commitment & acceptance tx effective. (Aims to improve functioning, rather than reducing pain; targets experiential avoidance; values emotional acceptance.)[270] 3) Multidisciplinary treatment programs: "showed modest improvement for specific outcomes measured. No relevant cost effectiveness studies of multidisciplinary treatment programs, for patients with chronic, nonmalignant pain in outpatient settings, were identified."[121] 4) Yoga: "Systematic review of evidence based guidelines and six individual guidelines include recommendations for yoga as a treatment for chronic pain"[122] *Chronic pelvic pain:* one study (n=60) showed that yoga 5x per week for 8 weeks significantly reduced VAS pain scores (6.7 to 3.4) when added to conventional pharmacological therapy (mainly NSAIDs) vs pharmacological therapy alone.[123] 5) Mindfulness: *Migraine or chronic tension-headaches:* Evidence to support the use of mindfulness (8 weekly sessions)[124,125] in addition to pharmacotherapy to decrease pain and increase quality of life vs pharmacotherapy alone. Effect appears to be lost if mindfulness practice is discontinued.[126]
II	In dementia, acetaminophen often 1st choice due to effectiveness & safety.[127,128,129]
III	NSAIDs: provide value in MSK pain over the short term; less benefit with longer term use.
IV	Amitriptyline: 75mg/d may be beneficial in Post-Stroke Pain 1 RCT (n=15).[130,131] **Chronic Primary Pain**: Consider an antidepressant (age >18) amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine, sertraline [NICE 253] Duloxetine: possibly effective for pain in major depressive disorder. Duloxetine 60mg/d improved pain (50% reduction) at 12 weeks in a meta-analysis (N=3, n=1359) RR~1.3.[59]
VI	Opioids: adding opioids to non-opioid therapy results in a reduction in pain, and an increase in function vs continuing established therapy without opioids.[1] Given 1000 patients with chronic pain treated over ≤6 months opioid therapy compared to continuing previous care: - Pain: 112 more patients would have a pain reduction of 1/10 on a VAS - Function: 102 more patients would have a small but important improvement There is no evidence of a dose-response effect for pain (p=0.49) or function (p=0.22).[1] Of note, based on observational data, although use of prescription opioids increased dramatically in the USA (104%, 2000-2010), this was not been accompanied by improvement in disability or health status metrics.[132] Opioids not recommended in some specific pain types such as chronic pelvic pain.[Choosing Wisely] **SUBOXONE**: based on 2 non-randomized studies & 1 retrospective study, an evidence-based guideline suggests **SUBOXONE** as being "effective, safe, unlikely to be misused, and highly useful for the treatment of chronic pain. It is also effective for hyperalgesia & addiction".[133] Dosage is usually BID-QID for pain therapy. Rheumatoid arthritis: Opioids appear to provide some benefits for pain,[134] but opioids do not prevent progression of the disease and should not be a replacement for an agressive DMARD strategy.
VII	Cannabinoids: Pain in general: limited evidence with mixed results; some may see improvement: meta-analysis (N=9) found patients more likely to report ≥30% improvement in pain (RR 1.43), but no difference when limiting to higher quality studies (i.e., longer duration and larger sample size). Additionally, a wide variation in product formulation and dosing complicated generalizability of results.[135] Spasticity: some benefit in MS with both **SATIVEX** THC:CBD buccal spray and smoked cannabis; however, also significant harms. (**see U-VII** Tolerability) Nabilone: some positive benefit & limited harms (studied dose range: 0.5-6mg/day).[136] Studies included MS, fibromyalgia peripheral neuropathy, post chemo- & radio-therapy, & medication overuse headache.
VIII	Lamotrigine: 200mg/d possibly effective in post-stroke pain based on 1 RCT (n=30).[137 138] Limited data on other anticonvulsants, and not routinely recommended.[139,140] Topical Compounded Creams: 1 RCT n=399, found no benefit vs pl (ketamine, gabapenitin, clonidine, lidocaine for neuropathic pain; ketoprofen, baclofen, cyclobenzaprine, lidocaine for nociceptive pain). [Brutcher 2019]

F: Sleep

I	Non-drug measures may include: sleep hygiene, sleep restriction, positioning & supportive supplies (e.g. pillows, splints), light therapy, daytime activity/exercise, bedtime routine, CBTi (may improve pain, too). {Note: *quality* of sleep more important than *quantity* of sleep.}
II-III	Acetaminophen & NSAIDs: may have some benefit on sleep if pain that is disrupting sleep.
IV	Amitriptyline: had some benefit on sleep vs duloxetine, but less than pregabalin. However, it was better tolerated and had fewer discontinuations due to adverse events.[58] Nortriptyline is an alternative to amitriptyline with potentially less AEs. Doxepin **SILENOR** 3-6mg (very low dose), is indicated for insomnia. Mirtazapine: 7.5-15mg may be an option for those with poor appetite, mood & sleep.[141] Trazodone: 25-100mg is potentially helpful in PDN & fibromyalgia. If SNRI (e.g. duloxetine) disrupts sleep, give early in day.
V	Pregabalin: improved sleep vs duloxetine, but had worsening function & more discontinuations due to adverse events (RCT in PDN at 4 weeks).[58]
VI	Opioids: sometimes problematic; at doses > 100 MED/d, opioids appear to cause sleep disturbance[142]; sleep apnea & additional mental health problems also a concern.[143]
VII	Selective cannabinoids (dronabinol [no longer available in CDN], nabilone, **SATIVEX** THC:CBD buccal spray) may have positive effect on sleep.[144] Cannabidiol (CBD) may have potential benefit in insomnia; however, delta-9 tetrahydrocannabinol (THC) may decrease sleep latency & impair sleep quality long-term.[145] Nabilone 0.5-1mg HS effective alternative to amitriptyline 10-20mg HS (1 RCT in fibromyalgia patients found sleep quality improved; preference for nabilone **NNT=11**).[107]
VIII	Other: adjuncts may be considered. (**See** RxFiles Sleep/Sedatives Chart). Insomnia may occur during opioid withdrawal; see Sedative chart page 193.

G: Overdose

II Acetaminophen: generally considered safe at recommended doses (≤4g/day); overdose possible with: a) acute ingestion of a high dose (≥ 200mg/kg or 10g); b) repeated supratherapeutic ingestion (over a 48 hour period: 150 mg/kg or 6 g/day (whichever is less) c) in the presence of risk factors (e.g. alcoholism, prolonged fasting/malnutrition, isoniazid use) overdose may present with repeated exposure to lower doses (100 mg/kg daily or ≤4 g/day). Unintentional overdose common due to cumulative exposure from ingestion of multiple &/or **combination OTC products** containing acetaminophen. (**see K** Hepatic Risk)
Note: some recent guidance, especially from the USA, suggests a max of ≤3g/day for chronic use.

III NSAIDs: higher doses are associated with higher risk of AEs. In overdose situations, monitor electrolytes & renal function, GI toxicity, and may consider activated charcoal.

IV Antidepressants: TCAs such as amitriptyline are potentially fatal in overdose; however, inadvertent overdose less common than currently seen with opioids. Uncertain, but venlafaxine may also be associated with increased risk of fatal overdose.[146,147]

V Gabapentin: associated with severe respiratory depression without concomitant opiates in up to 1 out 1000 patients based on post-marketing studies.[MHRA'17]

VI Opioids:[1] patients with CNCP who are on opioids are at risk of an overdose. The risk is greater for those with active depression, SUD (substance use disorder, active or history of), or on high MED regimens (e.g. >100 MED/day). Concurrent use of CNS depressants (e.g. alcohol, cannabinoids, benzodiazepines, gabapentin) also increases risk. Inadvertent overdose is a prominent current concern (*opioid crisis*). Evidence for dose-dependent harms is described in Table 1.

Other overdose risk factors:
- altering route of delivery (e.g., crushing, smoking or snorting pills, or injecting)
- obtaining opioids illicitly
- resuming opioid use after a period (e.g. 7+ days) of not consuming (e.g. after incarceration, during a taper), as previous tolerance is lost.

Tramadol: additional potential harms with overdose include seizures & serotonin syndrome.

Table 1: Dose-related Opioid Harms

Opioid Dose	FATAL Overdose Rate	Non-Fatal Overdose Rate
<20 MED/d	0.1%	0.2%
20-49 MED/d	0.14%	na
50-99 MED/d	0.18%	0.7%
>100 MED/d	0.23%	1.8%

VII Cannabinoids: overdose may present as drowsiness/impairment which may result in hospitalization. The ↑ potency of edible cannabinoids or THC oil products has led to an ↑ in overdose as well, especially but not exclusively in children.[148,149,150]

H: Mortality

II Acetaminophen: mortality secondary to overuse is rare overall & primarily associated with acute overdose. Overuse may be inadvertent due to multiple products with acetaminophen, or overuse of an acetaminophen/codeine combination (e.g. Tylenol #1) when attempting to get codeine component.

C Gabapentin: associated with increased risk of opioid-related death when gabapentin is combined with an opioid.[151]

VI Opioids: risk of all cause mortality appears higher for CNCP patients on opioids than for those on anticonvulsants or antidepressants.[152] There is an ↑ in non-fatal overdose risk (9x) in those at doses >100 MED/day, and overdose more likely to be fatal.[1,153] Between January 2015 and June 2019, there were 13,900 apparant opioid-related deaths in Canada.[154]

VII Cannabinoids: no RCT data. Cohort data unclear due to confounders. However, good evidence that cannabis use increases the risk of motor vehicle accidents.[155]

I: Addiction / Substance Use Disorder (SUD) Risk

V Gabapentin: abuse potential (snort or inject high dose for euphoria), or used to ease withdrawal from alcohol, cocaine. Some reports/concerns regarding opioid & gabapentin cross-abuse (potentiation of opioid; relaxed euphoria).[156] More likely with doses >3000mg/day Pregabalin: potential for abuse is a concern. MHRA (UK) has planned to move these agents to controlled drug status. FDA currently has pregabalin scheduled. Canada is aware, but has not changed schedule status.

VI Opioids: Hx of alcohol use disorder ↑ risk of opioid overdose, accidents, & injury rates.[157]
CDN Guideline Meta-analysis (9 studies, n=22,278 patients): risk of opioid addiction was 5.5% even when taking opioids as prescribed.[1] Addiction risk did not appear to be related to dose; but greater in those with active SUD or unstable psychiatric disorders. Tamper-Resistant or Abuse-Deterrent formulations are available (see Table 8); however, evidence regarding their value and role vary. May have some potential to reduce misuse & abuse (e.g. injection use); however, none deter abuse through oral ingestion of many tablets.[158,159]
Tramadol: lower potency opioid; no evidence of less addiction risk[160]; abuse ↑ in USA {about 250%, 2005 -2011 (6256 to 21,640 visits)}[161] Acute use associated with ↑use vs other short acting opioids.[231]
Tapentadol: potential for abuse similar to μ-opioid analgesics, such as morphine & hydromorphone; underestimation/low incidence due to limited availability & use.[162]

VII Cannabinoids: due to recreational use/abuse & high potency, medicinal marijuana may be problematic. Risk of developing dependence to cannabis was ~ 9% in one study.[163]
Observational data shows mixed results for the impact of medical/recreational cannabinoids on amount of opioid use, and/or opioid use disorder.[266,267]

J: Gastrointestinal (GI) Risk

III	NSAIDs: GI risk well appreciated in those with risk factors. Greater risk with higher doses, longer term therapy, & concomitant therapy with other drugs that increase bleeding. Consider prophylaxis (e.g. with standard dose PPI) in those at high risk. Topical NSAIDs associated with less risk than oral NSAIDs due to lower systemic levels.
VI	Opioids: GI adverse event risk is ↑d.[164] Observational OA trial in older adults saw an ↑ bowel obstruction with opioids vs NSAIDs (HR=4.87). Constipation very common! Esophageal dysfx.
VII	Cannabinoids: while some cannabinoids (i.e. nabilone) are indicated for severe nausea/vomiting from cancer chemotherapy, trials paradoxically often show an increase in nausea versus placebo (e.g. rates of nausea, vomiting, or diarrhea were 30% in the cannabis group and 21% in the control group after 1 year in the **COMPASS** trial). As well, *Cannabinoid hyperemesis syndrome* is a rare but serious adverse effect; discontinue cannabinoid and conisder topical capsaicin applied to stomach for symptomatic management.[165]

K: Hepatic Risk

II	Acetaminophen: (**see G-II** Overdose Risk) for those with chronic pain at ↑risk, consider monitoring LFTs (e.g. every 3-6 months). ↑risk if chronic/extensive alcohol use (≥ 3 drinks /day), those with liver disease, those who are malnourished, or others risk factors for hepatic disease.[166] Avoid or limit acetaminophen use (e.g. ≤2g/day) in those with cirrhosis.
III	NSAIDs: hepatic risk uncommon with most; ↑ LFTs/risk with diclofenac & sulindac.[167]
IV	Amitriptyline & Nortriptyline: hepatically metabolized; use with caution in hepatic dysfunction (no dosing adjustments specified in monograph). Venlafaxine: reduce dose by ~50% in mild to moderate hepatic impairment. Duloxetine: avoid in hepatic impairment.
VI	Tramadol: IR (**ULTRAM**): if cirrhosis, max dose recommended is 50mg q12h; ER (**ZYTRAM XL**, **TRIDURAL**, **RALIVIA**): avoid use if Child Pugh Class C; use caution if Child Pugh Class A/B. Opioids: drug exposure increases in cirrhosis, monitor and adjust dose as necessary. Buprenorphine mainly excreted via liver - use with caution.
VIII	Cyclobenzaprine: caution in mild hepatic impairment (~doubles drug exposure); consider starting at lower dose and/or less frequent dosing; avoid if moderate/severe impairment.

L: Renal Risk

III	NSAIDs: may use if CrCl ≥30mL/min or if dialysis; avoid if CrCl <30mL/min (unless dialysis) & in transplant patients. Choosing Wisely Canada: don't prescribe NSAIDs in individuals with chronic kidney disease of all causes, including diabetes.[168] Self-reported use not associated with renal injury/harm in otherwise healthy older adults.[250]
IV	Amitriptyline & Nortriptyline: renally eliminated; use with caution (no dosing adjustments specified in monograph). Venlafaxine: ↓ total daily dose by 25-50% dose if GFR ≤70mL/min. Duloxetine: avoid if CrCl <30mL/min or in dialysis.
V	Pregabalin: usual 600mg/day max; **CrCl 30-60mL/min** = 300mg/day max; **CrCl 15-30mL/min** = 150mg/day max; **CrCl <15mL/min** = 75mg/day max Gabapentin: usual 3600mg/day max; **CrCl 50-79mL/min** = 1800mg/day max; **CrCl 30-49mL/min** = 900mg/day max; **CrCl 15-29mL/min** = 600mg/day max; **CrCl <15mL/min** = 300mg/day max
VI	Tramadol: IR (**ULTRAM**): <30mL/min q12h dosing (max 200mg/d); ER (**ZYTRAM XL**, **TRIDURAL**, **RALIVIA**): <30mL/min avoid use. Morphine: metabolites may accumulate, causing AEs if CrCl <30mL/min. This is less of an issue at low doses; however, monitor & switch (e.g to hydromorphone) if problematic side effects.

M: Cardiovascular (CV) Risk[169]

III	Concern with all NSAID/COXIB: consider benefit/harm & select patients carefully; use lowest effective dose. – ↑ risk: diclofenac ≥150mg/day, indomethacin, celecoxib >200mg/day, meloxicam. – risk appears neutral[PRECISION]: naproxen ≤750mg/day, celecoxib[CONCERN] ≤200mg/day & ibuprofen ≤1200-?<2400mg/day.[170,171] **Choosing Wisely Canada**: don't prescribe NSAIDs in individuals with hypertension.[158]
IV	TCA: ↓ BP, ↑HR, widen QRS (overdose), prolong QT interval. Venlafaxine: ↑ BP and HR, prolong QT interval.
VI	Opioids: ↓ HR; tramadol, methadone and possibly oxycodone at higher doses – may prolong QT.[172]
VII	Cannabinoids: generally ↑ HR; variable effect on BP; inhaled marijuana associated with cardiovascular risk (may trigger an acute event).[173,174]

N: Heart Failure (HF) Risk

III	Oral NSAIDs: can exacerbate HF & lead to hospitalization due to Na^+ & water retention, ↑ systemic vascular resistance, ↑ BP, worsening renal function & diuretic resistance. [175,176,177] – Several heart failure guidelines recommend avoiding NSAIDs,[ESC'16 (IIIB), 178 ACCF/AHA '13 (IIIB)] or to use with caution. [CCS'06 (IB)] – **Choosing Wisely Canada**: don't prescribe NSAIDs in individuals with HF.[158] – The risk appears to be dose-dependent & can occur within days.[179] Topical NSAIDs: may also cause acute HF, but less likely compared to oral NSAIDs due to lower systemic levels. May use, but monitor HF status, weight, etc. – Only 6% of topical diclofenac is systemically absorbed (note: heat ↑absorption).[180] – Topical diclofenac does not appear to ↑ CV risk.[181,182] In an open-label RCT with 947 patients, topical diclofenac 1% 4g/day x 12 months did not ↑CV risk compared to placebo (10.2% had history of cerebrovascular or cardiovascular disease at baseline).[196]
IV	TCAs: may cause postural hypotension, which can limit the titration of ACEI, ARBs or ARNI target doses. These agents also have negative inotropic & proarrhythmic properties. Reversible upon discontinuation.[189] SNRIs: there are 2 case reports of venlafaxine & duloxetine worsening HF;[183] however, a 2014 observational study in Ontario found that low to moderate doses of venlafaxine were not associated with an increased risk of HF compared to sertraline.[184]
V	Gabapentinoids: can cause dose-dependent peripheral edema. An observational study from Ontario[2017] did not find an ↑ risk of HF with pregabalin use, compared to gabapentin.[185] Monitor weight/fluid status, & use with caution in patients with NYHA Class III or IV HF.
VI	Opioids: sleep disordered breathing (e.g. sleep apnea) in HF patients increases the risks of opioids & other centrally sedating medications.[186]
VIII	Gout is common in HF; avoid NSAIDs; consider corticosteroids or colchicine in acute gout.[187]

O: Seizure Risk[188,189,190,191]

III	NSAIDs: mechanism is unclear; NSAIDs potentially ↓prostaglandins which ↓seizure threshold. Reports with oral: indomethacin (50mg x1), ASA (500mg x1 or in overdose ?secondary to metabolic acidosis), diclofenac, mefenamic acid (toxic dose ≥60mg/kg). [192,193,194]
IV	Antidepressants: low risk at therapeutic doses (exceptions are: clomipramine & bupropion), but ↑ risk with overdose[195,196] e.g. venlafaxine dose dependent risk (≥900mg).[197,198]
V	Gabapentinoids: low risk, unless abrupt withdrawal in epileptic patients. Taper to stop.
VI	Opioids: all may ↑seizure risk; but especially tramadol (associated with seizures at therapeutic & toxic doses e.g. seizure in 8% of patients >500mg).
VII	Cannabinoids: cannabidiol likely effective in refractory pediatric Dravet syndrome to ↓ seizures.[199] In other seizure types, conflicting reports for both improving & worsening seizures.[200] Possibly increased seizure risk with increased THC potency.[201]
VIII	Baclofen: associated with seizure upon withdrawal (including status epilepticus).[202] Cyclobenzaprine: seizures rare; however, structurally similar to TCAs.

P: Falls and/or Fracture Risk

IV	Antidepressants (especially TCAs): may result in ↑ falls/fractures due to BP drop (greatest with amitriptyline), and/or CNS & ACh side effects (e.g. ↓ alertness, balance, dizzy).
VI	Opioids: have been associated with increased falls[203] & fractures[204,205] in observational studies. Those on ≥50 MED/d appear most at risk (HR=2). One OA study in older adults saw an ↑ in hip, humerus, pelvis, and wrist fractures (HR=4.47; **NNH=26/yr**) vs NSAIDs.[206] The first 2 weeks following initiation is a particularly high risk period for fractures.[207]
VIII	Caution with 3+ CNS drugs. CNS effects additive & ↑ falls, especially in elderly.[208,209] Review potential drug causes and explore non-drug fall prevention measures.

Q: CNS Adverse Effects (AE) - alertness, drowsy, dizzy, coordination, balance

III	NSAIDs: reports of cognitive dysfunction, esp in elderly. Most reports with indomethacin.[210]
VI	Opioids: opioids definitely have CNS side effects. However, when used at *steady low-moderate doses in chronic pain*, evidence suggests impairment may sometimes be minimal, or even improved. Caution![251]
IV-VIII	Antidepressants, gabapentinoids, opioids, cannabinoids, muscle relaxants: all notable for CNS AEs. Start low, go slow; use lowest effective dose; caution with polypharmacy (**see P-VIII** Falls and/or Fracture Risk); consider giving larger portion of daily dose in evening/HS; evaluate patient & adjust dose/regimen. Counsel patients that AEs diminish over ~3-10d when dose/regimen stabilized. Allow for adequate trial to assess tolerability. Note, for cannabinoids, CNS effects particularly associated with THC containing products.[254]

R: Anticholinergic Adverse Effects

II - VIII	Anticholingeric effects are common, especially with TCAs (amitriptyline > nortriptyline). Cannabinoids sometimes associated with dry mouth, especially THC containing products.[254] May manage dry mouth with a) non-pharmacological options, b) OTC saliva substitutes, or c) pilocarpine rinse. See RxFiles: Anticholinergics chart page 154 online at www.rxfiles.ca for management tools.

S: DIs (Drug Interactions)

III-VIII	Many of these medications have similar AE profiles and combinations may lead to potentiation of these AE, for example: **CNS**: TCAs, SNRIs, gabapentinoids, opioids, cannabinoids. Benzos & Z-drugs increase overdose risk of opioids[268] **ACh**: TCAs, opioids **Weight gain**: TCAs, gabapentinoids, cannabinoids **5HT** (i.e. serotonin syndrome): TCAs, SNRI, SSRIs, opioids (esp tramadol, tapentadol; fentanyl, methadone, oxycodone) **QT prolongation**: TCAs, ?SNRI, methadone, tramadol **GI bleeds**: NSAIDs, SSRIs	**Important drug interaction:** Ibuprofen/naproxen & ASA for CV prevention: consider alternate NSAID, or give NSAID 30 minutes after, or 8hrs before ASA. These NSAIDs can prevent ASA from fully achieving its full antiplatelet effect. **Important drug interaction**: Strong 2D6 Inhibitors: (such as fluoxetine, paroxetine, bupropion, terbinafine, quinidine) can ↓↓ effect of tramadol, codeine etc. [234]

T: Weight Gain (or Loss)

I	Non-drug treatment: interventions (e.g. exercise, dietary, ↑ activity) will help limit the weight gain often seen in deconditioned patients, or with drug therapy.
IV	TCAs: notable for weight gain, especially amitriptyline. Duloxetine may result in weight gain or weight loss.[211] Fluoxetine or bupropion option if treating depression/mood.
V	Gabapentin & Pregabalin: weight gain common with both agents.[212]
VI	Opioids: potential for weight gain or weight loss (particularly in overuse/abuse); when used at usual doses for pain, weight gain is seldom an issue.
VII	Cannabinoids: weight gain possible side effect (? due to ↑ appetite). **General:** Deconditioning is common in CNCP patients; give attention to diet & exercise.
VIII	Topiramate: potential for weight loss, if otherwise tolerated (setting of neuropathic pain, or migraine prevention). See Weight Loss chart.

U: Tolerability

III	Topical NSAIDs: very well tolerated, with AE rates similar to placebo.
IV	Antidepressants: all except nortriptyline escalating doses of 25-100mg/day had AE>placebo.[213] Duloxetine: may be associated with a higher rate of discontinuation due to AE especially at >60mg/d (**see A-IV** LBP, **C-IV** Neuropathic Pain, & **D-V** Fibromyalgia). **PEER**: Discontinuation due to AE: antidepressants in neuropathic pain SNRIs duloxetine, venlafaxine: NNH=13; TCAs NNH=12.[265] AEs of antidepressants generally reversible & NOT associated with any structural organ damage. RCT with amitriptyline 75mg/day, duloxetine 120mg/day, pregabalin 600mg/day & placebo in PDN found equal analgesia, but differences in tolerability (equal QOL; pregabalin worse for daytime functioning, ↑D/C due to AEs, but better effect on sleep per polysomnograph).[58]
V	Gabapentinoids: CNS side effects, especially dizziness & somnolence, are common. Pregabalin: may be associated with a higher rate of discontinuation due to AE especially at >300mg/d (**see D-V** Fibromyalgia). **PEER**: Discontinuation due to AE: anticonvultants in neuropathic pain Gabapentin NNH=22, Pregabalin NNH=17, Topiramate NNH=7. [265]
VI	Opioids: as doses increases, serious harms also increase.[214] A systematic review of predominately uncontrolled trials ≥6 months found ~30% of oral opioid users discontinued therapy due to AE or lack of benefit.[215] In the **PEER** SR for neuropathic pain, potential for harm (NNH=12) rivals benefit.[265] **Set Functional Goals & Monitor!**
VII	Cannabinoids: numerous formulations available with varying potency and toxicity. Common dose dependant AEs: dizziness, sedation, confusion, dissociation, euphoria. - Potential increase risk of: [216] motor vehicle collisions, mania in non-bipolar population, psychosis, ? cognitive dysfunction. Other, serious uncommon AE: ↑ infectious disease complications (e.g. aspergillosis).[217,218] **Set Functional Goals & Monitor!**
VIII	**PEER:** Discontinuation due to AE: Topical Capsaicin in neuropathic pain NNH=25.[265] Combos: caution with combining systemic agents that affect the CNS: cummumlative CNS AEs

V: Psychiatric Disorders

I	Non-drug treatment: several non-drug therapies (e.g. CBT, mindfulness) are effective & valuable in treating psychiatric disorders - see psychhealthandsafety.org/pcwhc.
III	NSAIDs: **indomethacin** & potentially sulindac are associated with acute disorientation, paranoia, or hallucinations, which is more common in older adults.[219]
IV-V	Antidepressants and gabapentinoids have significant CNS & anticholinergic AEs and extra vigilance is warranted in older adults due to the potential for causing delirium.
VI	Opioids: low quality evidence suggests ↑risk of very serious AEs (non-fatal overdose & death) in patients with serious psychiatric disorder.[1] Addiction risk also ↑.[1] Stabilizing psychiatric disorder advised before considering an opioid trial.[1] Use caution in older adults due to the potential for causing delirium. ?Hallucinations with tramadol (esp. age>65).[239] Depression/anxiety/mood disorder: common comorbidity in opioid users;[220] caution necessary when prescribing opioids in this population.
VII	Cannabinoids: data from the one year **COMPASS** trial showed a 27% risk of psychiatric disorders (vs 11% in control group, **NNH=6**), including depression, anxiety, euphoria, panic attack, paranoia, apathy, & hallucination.[155] Use caution in older adults due to the potential for causing delirium. One SR (N=46, n=6216) found safe in those over age 50.[254] Evidence for benefit in post-tramatic stress disorder (PTSD) is inconclusive.[221]

W: Pregnancy/Lactation (Risk symbols from RxFiles Comparison Charts)[222]

Safe / Likely Safe / Caution / Contraindicated

II	Acetaminophen: possible association with behavioural & hyperkinetic disorders.[223]
III	Oral NSAIDs: [224,225,226] ? block implantation, miscarriage, malformations, premature ductus arterious closure, cryptorchism, inhibit labour, fetal renal toxicity. Topical NSAIDs: in general, safer than oral NSAIDs
IV	TCA: more experience vs SNRIs; ↓ levels in breastmilk (<10% maternal dose)
V	Gabapentinoids: Limited data (more with gabapentin vs pregabalin). Monitor baby for drowsiness, poor feeding/weight gain if breastfeeding. Risk of fetal malformations and intrauterine death similar to general population, but associated with low birth weight.[227,228]
VI	Opioids:[229] In the third trimester, ≥30 days of use may cause neonatal respiratory depression & opioid withdrawal. Abrupt D/C may cause premature labour & spontaneous abortion. Taper to lowest effective dose. Codeine, tramadol – ↑toxicity risk in ultra-rapid CYP2D6 metabolizers (FDA warning);[230] Monitor baby for limpness, difficulty breathing/feeding, or ↑ sleep. Oxycodone: One study in 2012 appeared to show more CNS depression with oxycodone than codeine in breast-fed infants whose mothers took an opioid.[231]
VII	Cannabinoids: Associated with impaired neurodevelopment, ?stillbirth, & ?↓ fetal growth. Lactation: insufficient data. Discourage use during preconception, pregnancy, lactation. [232] ACOG'15

	1st Trimester	2nd Trimester	3rd Trimester	Lactation
Acetaminophen				
Ibuprofen, Naproxen, Celecoxib				
Ketorolac				
Topical NSAIDs			?	
Gabapentin				
Codeine, Tramadol				
Oxycodone				
Morphine, Fentanyl, Hydromorphone				
Methadone	For discussion, see page 136			
Buprenorphine/naloxone				
Duloxetine				
Nortriptyline				
Cannabinoids				

X: Cost per Month see Pain Medication Dosages, Regimens, Options & Costs, see page 128

I	Non-drug treatment: some can be inexpensive & built into routine/lifestyle. Others can be quite costly. Success requires availability, affordability, & coordination. Multidisciplinary team approaches are part of many successful interventions; unfortunately this type of support is not always available (or affordable).
II	Acetaminophen: acetaminophen 650mg q6h ($5); extended release **TYLENOL ARTHRITIS** 1.3g q8-12h ($20)
III	Oral NSAID: Naproxen 375mg BID ($20) Topical NSAID: OTC diclofenac ($26) 2x150g; Prescription diclofenac $26-92; Compounded 3-10% diclofenac or ketoprofen cream/gel is on NIHB formulary ▼.
IV	Antidepressants: Amitriptyline 75mg HS ($23); Venlafaxine 150mg daily ($22); Duloxetine 60mg daily ($42)
V	Gabapentinoids: Gabapentin 600mg TID ($42); Pregabablin 150-225mg BID ($48-76)
VI	Opioids: Tramadol ($45-167) (**TRIDURAL** - **ZYTRAM XL**); Morphine SR 30mg q12h ($33), 60mg q12h ($51); Hydromorphone SR 6mg q12h ($81), 12mg q12h ($133)
VII	Cannabinoids: Nabilone ($112); **SATIVEX** ($240/vial) *CanniMed*(SK dispensary): **Dried**: 1.5g/d ($200-400)avg dose 2.5g/d in **COMPASS** **Vaporizers**: ($229-669) **Oil**: 60mL bottle ($129-169) [may last some on low doses e.g. 0.5mL/d up to 3 months]

Y: Other

I Non-drug treatment:

- Pain reduction and improved function, not pain elimination, is the goal of drug therapy. Those with CNCP must be helped to refocus on positive, incremental gains. Dedicated therapists &/or CNCP programs are helpful.
- Address Fear/Avoidance of Physical Activity: fear-avoidance beliefs hold a stronger relation to disability & poor pain rehabilitation outcomes than does pain intensity.
- Education, behavioural, psychosocial, physical & other therapies (e.g. music) are essential for successful long-term management. **Encourage "self-help" approaches.**
- Consider role of concomitant: exercise, pacing, heat, ice, TENS, CBT, relaxation, spiritual, ↓music therapy, acupuncture, yoga, massage, tai chi etc.
- Multidisciplinary interventions may ↓ drug requirements. Programs that simultaneously address physical, psychological & functional aspects may be needed for some.

VI Opioids: several potential dose dependent AEs with *higher-dose*, *long-term use*. **Hyperalgesia**, where there is a central sensitization to pain, may result in loss of effectiveness. Effectiveness may return after deprescribing the opioid. High doses (e.g. ≥120 MED/d) of opioids associated with lower testosterone & need for treatment if symptomatic.[233] May be other potential concerns: e.g. pancreatic ca? [247]

Opioid patient education: Navigating Opioids for Chronic Pain: https://www.cpd.utoronto.ca/opioidprescribing/navigating-opioids/ Best Advice for People Taking Opioid Med (Doc Mike Evans): www.youtube.com/watch?v=7Na2m7lx-hU

FDA warnings (opioids in general)

- Opioids can interact with antidepressants and migraine medicines to cause serotonin syndrome. Patients taking an opioid along with a serotonergic medicine should seek medical attention immediately if they develop symptoms such as agitation; hallucinations; rapid heart rate; fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea
- Taking opioids may lead to a rare, but serious condition in which the adrenal glands do not produce adequate amounts of cortisol. Patients should seek medical attention if they experience symptoms of adrenal insufficiency such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.
- Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility.
- Serious risk of breathing difficulties leading to death when combined with benzodiazepines, gabapentionoids, or other drugs that depress the central nervous system.

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DURAGESIC	128
EFFEXOR	128
ELAVIL	128
EMULGEL	128
Fentanyl	128
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Gabapentin	128
HYDROMORPH CONTIN	128
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Diabetic Peripheral Neuropathic Pain (DPNP)
Amitriptyline vs Duloxetine vs Pregabalin vs Pl

- Double-blind, RCT, parallel group
  - n=83, ~65yo, DM $_{T1/T2}$ x14yrs, A1C=7.9%
    - Age 18+, DPNP (clinical + Leeds Assess confirmation), ~2/3 male, BMI=32, 87% T2DM, Caucasian
  - 8 day placebo run-in
  - Initial Tx x14 days ➔ Target Tx x14 days
    - **Amitrip** 25mg BID ➔ **25mg am, 50mg HS**
    - **Duloxetine** 60mg am ➔ **120mg daily am**
    - **Pregabalin** 150mg BID ➔ **300mg BID**
  - Allowed opioids, NSAIDs, acetaminophen
  - Funding: investigator led grant from Pfizer

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DPNP – Trial Results – over 4wks
Amitriptyline vs Duloxetine vs Pregabalin vs PL

Drug & dose/day	Amitript ELAVIL 75mg/d	Duloxetine CYMBALTA 120mg/d	Pregabalin LYRICA 600mg/d
1° Pain BPI, VAS	-/+	-/+	-/+
Sleep Subjective	-/+	-/+	-/+
Sleep, PSG (polysomnogram)	✓	✗ ↓sleep, ↑WASO, ↓REM	✓ ✓ ↓PLM, ↑AHI
Function Day	✓	✓	✗
QOL SF-36	-/+	-/+	-/+
AEs Tx related	✓ 1 withdrew	✓ 3 withdrew	✗ 6 withdrew fatigue, dizzi,drowsy

AHI=apnea/hypopnia index, PLM=periodic limb movements, REM=random eye movement sleep, WASO=wake after sleep onset. Color code: Dark Green=BEST; Light Green=Better; Yellow=no difference; Orange=worse

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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 ✗ ▼ Immediate release caplet/tablet: 160, 325, 500mg ✗ ▼ PL Extended release caplet: TYLENOL ARTHRITIS 650mg ✗ ⊗ Gelcap: 500mg ✗ ⊗ Drops: 80mg/mL ✗ ▼ Liquid: 16mg/mL, 80mg/mL, 32mg/mL ✗ ▼ Suppository: 120, 160, 325,650mg ✗ ▼ {IV: 1000mg/100ml bag ✗ ⊗} ▼ **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 $7-18	**NON-ANTI-INFLAMMATORY ANALGESIC** • Compared to NSAIDs/COXIBs, lowest risk for CV events & GI ulcer/bleed • Option in osteoarthritis • **DI**: 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** ✗ ⊗

Combination Anagesic:

COMBOGESIC tab = acetaminophen 325 mg + ibuprofen 97.5 mg, 1 or 2 every 6 hours. (Note, could take up to 3 tabs at one time.off-label Consider higher cost.)

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.
- **disintegrating meloxicam** (**QMIIZ ODT**) Not in Canada – 7.5mg, 15mg tablets 15mg ODT bioequivalent to the 15mg conventional oral meloxicam tablet. Disintegrates rapidly; does not require administration with liquid.

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

Acetylsalicylic Acid	129
ADVIL	**129**
ALEVE	**129**
ANAPROX	129
ANSAID	129
ARTHROTEC	129
ASPIRIN	129
CAMBIA	129
CELEBREX	**129**
Celecoxib	**129**
CLINORIL	129
COMBOGESIC	129
COXIB	129
DAYPRO	129
Diclofenac	**129**

Diflunisal	129
DOLOBID	129
EMULGEL	129
ENTROPHEN	129
Etodolac	129
FELDENE	129
Fenoprofen	129
Floctafenine	129
Flurbiprofen	129
Ibuprofen	**129**
IDARAC	129
INDOCID	129
Indomethacin	129
Ketorolac	129
Lumiracoxib	129
Mefenamic Acid	129
Meloxicam	129
MOBICOX	129
MOBIFLEX	129
MOTRIN	**129**
Nabumetone	129
NAPROSYN	**129**
Naproxen	**129**
ORUDIS	129
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Pain	**129**
Piroxicam	129
PONSTAN	129
RELAFEN	129
Rofecoxib	129
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PENNSAID	129
NSAIDs	129
NSAID-Topical	129
Ketoprofen	129
ASA	129

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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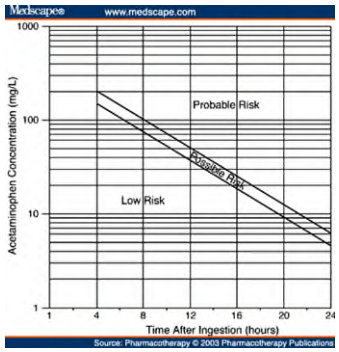
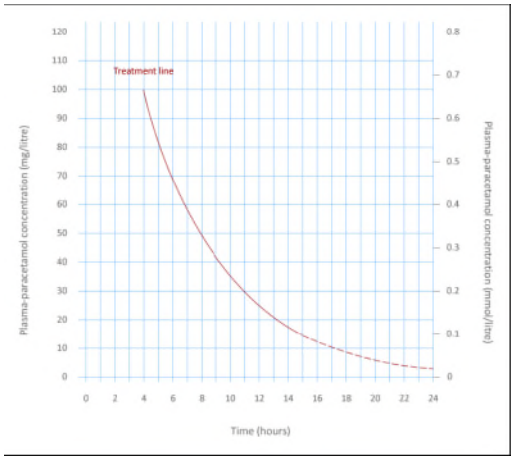


MHRA Sept 2012: Paracetamol (acetaminophen) overdose: Simplification of the use of intravenous acetylcysteine



{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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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.
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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.
Health Canada June/17: **PHQ 1001 Khasiat Penawar Herba Qaseh Serata Herb** has undeclared dexamethasone, piroxicam, griseofulvin and paracetamol by Singapore Health Sciences Authority.
Health Canada June/17: **TONIK TUAN HAJI 1921** has undeclared dexamethasone by Hong Kong Department of Health.
Health Canada June 2021 has completed a safety review confirming that the use of non-steroid anti-inflammatory drugs (NSAIDs)—such as acetylsalicylic acid (aspirin), ibuprofen, naproxen, diclofenac and celecoxib —starting from **approximately 20 weeks of pregnancy** or later may cause rare but serious kidney problems in an unborn baby. This can lead to low levels of amniotic fluid and possible complications, such as impaired lung maturation and loss of joint **movement (limb contractures) in the newborn baby.**
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with rofecoxib (RR 1.25; 95% **CI 1.17 to 1.34**) but not with any other NSAIDs. Four RCTs of NSAIDs in colonic adenoma (6000 patients) showed an increased risk of MI (RR 2.68; 95% CI 1.43 to 5.01). Fourteen RCTs in arthritis (45 425 patients) showed more MIs with cyclo-oxygenase-2-specific drugs (Peto OR **1.6**; 95% CI 1.1 to 2.4), but fewer serious upper gastrointestinal events (Peto OR 0.40; 95% CI 0.31 to 0.53). CONCLUSION: The overall risk of MI with NSAIDs and cyclo-oxygenase-2-specific drugs was small; rofecoxib showed the highest risk. There was an increased MI risk with cyclo-oxygenase-2-specific drugs compared with NSAIDs, but less serious upper gastrointestinal toxicity.}

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Acetaminophen + Codeine	**130**
ACTIQ	130
AMITIZA	130
ASA/Codeine/Caffeine	130
AVINZA	130
Buprenorphine	**130**
Buprenorphine + Naloxone	**130**
BUTRANS	**130**
Codeine	**130**
CODEINE CONTIN	**130**
DEMEROL	**130**
DILAUDID	**130**
DOLORAL	130
Domperidone	130
DURAGESIC	**130**
EMTEC-30	130
Fentanyl	**130**
FENTORA	130
Haloperidol	130
HYDROMORPH CONTIN	**130**
Hydromorphone	**130**
JURNISTA	130
KADIAN	**130**
Lactulose	130
Lubiprostone	130
M.O.S.	130
M-EDIAT	130
Meperidine	**130**
M-ESLON	130
METADOL	130
Methadone	**130**
Methylnaltrexone	130
Metoclopramide	130
Morphine	**130**
MOVANTIK	130
MS-CONTIN	**130**
MS-IR	130
Naloxegol	130
Narcotic	130
NUCYNTA	**130**
Opiate	**130**
Opioid	**130**
Oxycodone	**130**
OXYCONTIN	130
OXY-IR	130
OXYNEO	130
Pain	**130**
Pentazocine	130
PERCOCET	130
PERCODAN	130
PROBUPHINE	130
Prochlorperazine	130
Propoxyphene	130
RALIVIA	130
RELISTOR	130
Senna	130
STATEX	130
SUBLOCADE	130
SUBOXONE	130
Sufentanil	130
SUPEUDOL	130
TALWIN	130
Tapentadol	130
TARGIN	130
TRAMACET	130
Tramadol	**130**
TRIDURAL	130
TYLENOL #3	130
TYLENOL #4	130
ULTRAM	130
ZYTRAM	130
SENOKOT	130

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**), (EXTAMPZA ER: capsules with microspheres of oxycodone base 9,13.5, 18, 27, 36 mg oxycodone)
- **Oxycodone** (ROXYBOND) - **USA**: abuse deterrent immediate release form; 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.
- **Tramadol/dexketoprofen** (SKUDEXA): 75mg/25mg; available in **UK**; indicated for moderate to severe acute pain; studied on post-op acute pain; max 5 days.
- **Tramadol Oral Solution** (Qdolo): 5mg/mL oral solution; available in **USA**; allow for gradual dose titration.
- **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 $_{diphenhydramine}$ +/- H2 $_{ranitidine}$ 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
4. **Tramadol and tapentadol** are structurally similar

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

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.

FDA Apr/17 is **restricting the use of codeine and tramadol medicines in children**. These medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. These medicines should also be limited in some older children. Single-ingredient codeine and all tramadol-containing products are FDA-approved only for use in adults. FDA is also recommending against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.

FDA Sep/17 is advising that the opioid addiction medications **buprenorphine and methadone** should not be withheld from patients taking **benzodiazepines** or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction usually outweighs these risks.

FDA Jan/18 is requiring safety labeling changes for prescription cough and cold medicines containing **codeine or hydrocodone to limit the use of these products to adults 18 years and older** because the risks of these medicines outweigh their benefits in children younger than 18. FDA is also requiring the addition of safety information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing to the Boxed Warning, the most prominent warning, of the drug labels for prescription cough and cold medicines containing codeine or hydrocodone.

FDA Apr/19 has received reports of serious harm in patients who are physically dependent on opioid pain medicines suddenly having these medicines discontinued or the dose rapidly decreased. These include serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide.

FDA Apr/19 Alvogen, Inc. is voluntarily recalling two lots of Fentanyl Transdermal System 12 mcg/h transdermal patches to the consumer level. A small number of cartons labeled 12 mcg/h Fentanyl Transdermal System patches contained 50 mcg/h patches. The 50 mcg/h patches that were included in cartons labeled 12 mcg/h are individually labeled as 50 mcg/h.

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that withdrawal symptoms may resolve more quickly with buprenorphine.It is not possible to draw any conclusions from the available evidence on the relative effectiveness of different rates of tapering the buprenorphine dose. The divergent findings of studies included in this review suggest that there may be multiple factors affecting the response to the rate of dose taper. One such factor could be whether or not the initial treatment plan includes a transition to subsequent relapse prevention treatment with naltrexone. Indeed, the use of buprenorphine to support transition to naltrexone treatment is an aspect worthy of further research.Most participants in the studies included in this review were male. None of the studies reported outcomes on the basis of sex, preventing any exploration of differences related to this variable. Consideration of sex as a factor influencing response to withdrawal treatment would be relevant research for selecting the most appropriate type of intervention for each individual.

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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.
Health Canada Jun/17 is advising health care professionals and Canadians that the **Canadian authorized version of NARCAN** will transition onto the market by July 5, 2017.
Health Canada Dec/17 held a Scientific Advisory Panel on Opioid Use and Contraindications, to consider whether the current contraindications for opioid use are sufficient, or whether labelling updates and other actions may be needed to reduce risks to Canadians. After thoroughly assessing the Panel's recommendations, Health Canada is working with manufacturers to update the Canadian labelling of all prescription opioid products. **Recommendation for a daily opioid threshold dose for the management of chronic non-cancer, non-palliative pain (which aims to reduce risks of adverse events and overdoses associated with taking higher doses of opioids); Recommendation to limit the quantity of opioids prescribed for acute pain** (which aims to reduce the duration of use and associated risks of developing dependence and substance use disorder); and Clarification of warnings, including those for special populations such as **pregnant women and patients with a history of dependence or substance use disorder**.
Health Canada Dec/17 is advising Canadians of the potential limitations when using **test strips to detect fentanyl**. A preliminary study undertaken by Health Canada indicated that false negatives could occur when using fentanyl-detection test strips. A false negative would be a test result that does not detect the fentanyl in a drug sample even though it does contain fentanyl
Health Canada June/18: Health Canada reminds Canadians of the **limitations of fentanyl test strips** being used to check street drugs before consumption.
Health Canada Sep/19 is advising Canadians about the increased risk of opioid overdose and **serious side effects when taking gabapentin (e.g., Neurontin) or pregabalin** (e.g., Lyrica) with an opioid.
Health Canada Mar/20: has received reports from patients and healthcare professionals that there may be variations in how patients respond to different formulations of methadone when used for opioid substitution treatment in opioid drug dependence.

Health Canada Aug/20 is advising Canadians that people **under 18 years of age should not use non-prescription pain relief products containing codeine**.
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Table 7. My patient is pressuring me to start or continue opioids. How do I say "no" while maintaining a positive relationship?[6] May 2021

"If you feel starting a prescription for an opioid might not be a good idea for your patient at any point in a consultation, you have an opportunity to stop and communicate to the patient your concern and reasons around not initiating opioids. Although it may be uncomfortable at first to say no, in the long run you are doing your patient a great service and practicing compassionate, evidenced-based medicine." -Sarah Liskowich, MD, CCFP

Use active listening skills. Sit with the patient to bring you to the same level. Listen to the patient's story, and reflect his/her words back to show that you're listening. Ask questions with a neutral tone. Does he or she perceive a large benefit with opioids? Are his or her expectations unrealistic (e.g. a goal of "zero pain")? Do opioids provide an "escape" from difficult life circumstances? Is there fear of withdrawal, or fear of unmanageable pain? Ensure your patient knows that you care about him/her, and want him/her to do well.	*-It sounds like there's a lot of stress in your life right now.* *-You're saying the pain is making you feel desperate and edgy.* *-I know you're going through a tough time right now, and I'm really sorry about that.*
Where possible, gather objective facts. These may include: pain scores over time, assessment of changes in function, adverse effects, previous history, risk of overdose or addiction (e.g. calculation of ORT score), presence of pain catastrophizing (e.g. www.painbc.ca/sites/default/files/events/materials/Pain_Catastrophizing_Scale.pdf). This is also where documentation of warning signs (e.g. requests for early refills, see Table 4) is important. Involving a colleague for a second opinion can also bring in valuable information. In the absence of objective facts, consider no therapy changes for a short period (e.g. 3 months) with clear criteria for how a decision will be made after that time.	*-It is my professional responsibility, in providing the best possible patient care, to only prescribe medications when it can be done safely.* *-I cannot in good conscience prescribe a medication that could harm or kill you.* *-You've told me Dilaudid works, but what else have you tried?* *-Before moving ahead, I will need to obtain and consider the initial assessment report regarding your accident and resulting injuries.* *-I haven't met you before, and can't prescribe these types of drugs on the first visit before I have a full history.*
Use the patient's history +/- objective facts to explain your decision. Sometimes focusing on the safety issues of opioids can be valuable (e.g. risk of overdose, presence of adverse effects). It is also helpful to reframe the goal from "pain relief" to "function restoration." It's OK to be honest and straightforward about your reasons for wanting to stop or avoid opioids; in fact, the situation can be viewed as an opportunity to educate patients. **If you are feeling emotionally pressured, or threatened,** it's OK to excuse yourself from the room and/or confer with a colleague. Avoid responding to emotion with emotion, and avoid prescribing emotionally. Try to keep your feelings and the medical facts separated. Be clear and consistent about expected boundaries for how you and your staff need to be treated. (What is expected, and what the consequences are if boundaries crossed.)	*-It looks like opioids aren't working well for you. I have noticed that...* *-This opioid seems to be doing more to you, than for you.* *-When we first started opioids, your pain was not controlled. Now you are on a high dose of opioids and having side effects ... but your pain is still not controlled. It might seem hard to believe, but if we pull back on the opioids you may actually feel better than you do now.* *-When I look at your medical history and other medical conditions, I worry that your risk of overdose with this medicine is too high.* *-If we combined an opioid with your sleep apnea, it could slow down your breathing too much, even to the point of stopping.* *-From what you've told me, I think stress is adding to your pain, and an opioid is not the best way to treat that problem.* *-In the long run, opioids will actually change the way your brain perceives pain. Numbing the pain for a while will make it worse when you finally feel it.*
Provide an alternate plan to show that you still support your patient. Encourage non-pharmacological therapies; offer non-opioid medications. Potentially, advise the patient that the pain may resolve on its own without opioids. Referring to a colleague for a second opinion may be helpful. Refer to an addictions medicine specialist if necessary. If discontinuing an opioid, provide reassurance that the opioid will be tapered slowly to prevent withdrawal symptoms and adjuvants prescribed as needed. Aim to be polite but firm!	*-We've talked about some options that may help you control your pain. Out of all those, what would you like to try?* *-There is a strong connection between feeling down and pain. Would you be willing to meet with our mental health specialist?* *-In the meantime, let's work together with your pharmacist on a gradual tapering plan.* *-I know you can do this, and I'll stick with you through it.*

Table 8: Formulations designed to help deter abuse[13]

- **Tamper-resistant formulations to deter injection**: **OxyNEO** (oxycodone), **NUCYNTA** (tapentadol), **TARGIN** (oxycodone/naloxone), **SUBOXONE** (buprenorphine/naloxone)
- **Once daily products to facilitate directly-observed therapy**: **KADIAN** (morphine), **JURNISTA** (hydromorphone)
- **Patches to couple with patch-exchange**: **DURAGESIC** (fentanyl), **BUTRANS** (buprenorphine)

References available online at www.RxFiles.ca

Additional Useful Links / Phone Numbers

★ Canadian Clinical Guidelines: www.cfpc.ca/2017_canadian_guideline_opioids_chronic_non_cancer_pain
★ American CDC Clinical Guidelines: www.cdc.gov/drugoverdose/prescribing/guideline.html
★ Patient Handout: www.ismp-canada.org/download/OpioidStewardship/opioid-handout-bw.pdf
★ Pocket Guide for Tapering: www.cdc.gov/drugoverdose/pdf/clinical_pocket_guide_tapering-a.pdf
★ ISMP Prescribing Tips: www.ismp-canada.org/download/OpioidStewardship/Opioid-Prescribing-Skills.pdf
★ Drug Information service for Saskatchewan clinicians: medSask 306-966-6340 or 1-800-667-3425
★ Saskatchewan Provincial Lab – (Urine Drug Screens): 306-787-3131

Link to RxFiles CFP Article "Tapering Opioids Using Motivational Interviewing" Aug 2018: https://www.cfp.ca/content/64/8/584

See also RxFiles:

- **Pain Approaches - Distinctives for the ACUTE vs PALLIATIVE vs CNCP use of Opioids:**
  - **http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Pain-Approaches-Acute-Palliative-CNCP.pdf**
- **RxFiles Pain & Opioid Links:**
  - **http://www.rxfiles.ca/rxfiles/uploads/documents/RxFiles-Pain-and-Opioid-Resource-Links.pdf**
- **RxFiles PainLinks (for patient resources& support services):**
  - **http://www.rxfiles.ca/rxfiles/uploads/documents/PainLinks.pdf**

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Prescribing Opioids Safely – RxFiles Chart - **http://www.rxfiles.ca/rxfiles/uploads/documents/members/Prescribing%20Opioids%20Safely.pdf**

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Opioid Conversion Equivalency Table(s): 1) Stanford Pall Care https://palliative.stanford.edu/opioid-conversion/equivalency-table/ ;

Thank you to Dr. Marwah for contributing to the review of this chart.

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Opioid Agonist Therapy: Colour Comparison Chart

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Cost Calculation for OAT:

Cost for methadone

- Drug: ~$1.00
- Mark-up: 10% ($0.10)
- Compound fee: $15.00
- Dispensing fee: $11.60
- =$27.70

- $3.50/witnessed dose
- Max 1 dispensing fee per 7 days
- Max 1 compounding fee per 7 days

For weekly dispenses – 28 days total (4 witnessed doses, 24 carries):

- $27.70 x 4 = $110.80
- $3.50 x 4 = $14.00
- =$124.80

For daily dispenses – 28 days total (28 witnessed doses, 0 carries)

- $27.70 x 4 = $110.80
- $3.50 x 28 = $84.00
- =$194.80

Cost for Bup-nal

- 12mg daily 8mg ($2.36) + 2x2mg ($1.34) = $5.04 x 7 days = $35.28
  - Mark up = $3.52
  - Dispensing fee = $11.60
  - =$50.40
- 16mg daily 2x8mg ($2.36) = $4.72 x 7 days = $33.04
  - Mark up = $3.30
  - Dispensing fee = $11.60
  - =$47.94
- 24mg daily 3x8mg ($2.36) = $7.08 x 7 days = $49.56
  - Mark up = $4.96
  - Dispensing fee = $11.60
  - =$66.12

- $3.50/witnessed dose
- Max 1 dispensing fee per 7 days

For weekly dispenses – 28 days total (4 witnessed doses, 24 carries):

12mg

- $50.40 x 4 = $201.60
- $3.50 x 4 = $14.00
- =$215.60

16mg

- $47.94 x 4 = $191.76
- $3.50 x 4 = $14.00
- =$205.76

24mg

- $66.12 x 4 = $264.48
- $3.50 x 4 = $14.00
- $278.48

For daily dispenses – 28 days total (28 witnessed doses, 0 carries)

12mg

- $50.40 x 4 = $201.60
- $3.50 x 28 = $84.00
- =$285.60

16mg

- $47.94 x 4 = $191.76
- $3.50 x 28 = $84.00
- =$275.76

24mg

- $66.12 x 4 = $264.48
- $3.50 x 28 = $84.00
- =$348.48

Opioid Use Disorder: Online Extras

Other Treatment Options/Adjuncts in OUD

Generic/TRADE	Comments	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitoring M	Initial, Usual & Maximum Dose	$/30 days
OPIOID AGONIST: Relieve withdrawal symptoms and reduce cravings by occupying (and stimulating) opioid receptors OUD *				
Slow Release Oral Morphine (SROM) PL **KADIAN** ✆ 10, 20, 50, 100 mg cap	• **Little evidence and not generally recommended!!** • May be a safer and effective alternative to methadone, and potentially be superior to methadone in reducing cravings, symptoms of dysthymia, and improved overall patient satisfaction;[13] however there is a paucity of evidence directly comparing against buprenorphine and methadone, therefore it is only recommended as a **second line agent** when bup-nal or methadone are ineffective or contraindicated.[9] • Commonly used for OUD in Europe.[13] • Only **KADIAN** (**24 hour**) morphine formulations are recommended for OUD. • Note: it has **high diversion potential** and thus is seeing less use in the OUD context. If used, daily witnessed ingestion would be highly recommended. (Look for cheeking.)	**CI**: Respiratory insufficiency, acute alcoholism, convulsive disorders, MAOI use within 14 days, GI obstruction **AE**: Nausea, constipation, dyspnea, sedation, confusion/CNS effects, sweat, miosis, **DI**: CNS depressants **M**: Regular urine drug screen (monthly during initiation and dose escalation) **Observed once daily dosing** when possible	**Initial:** Based on morphine equivalent dose. 30-60mg po daily for heroin users.[9] For methadone, use 1:4 ratio, e.g. 60mg methadone=240mg **KADIAN**. **Usual:** 60-600mg po daily[9] **Maximum:** 1200mg po daily[9]	$90-500 $987
OPIOID ANTAGONIST: ↓ euphoric effective of opioids				
Naltrexone ☎ ▼ **REVIA**, g 50mg tablet **VIVITROL** FDA, SAP 380mg IM Depot (not readily available in Canada)	• Fully blocks opioid receptors, therefore patient must not be using any opioids (including OAT and pain management). It does not have any abuse potential.[18] • Oral naltrexone **has limited benefits over placebo for opioid abstinence and retention rates in patients who received withdrawal management only**.[9] Patients must be opioid free for 7-10 days, and many patients relapse before naltrexone can be started.[16] • Can be considered in patients who have successfully ceased opioids (including OAT or slow taper) to prevent relapse,[7,13] and in patients **with concurrent alcohol use disorder** (AUD); (see RxFiles Alcohol Use Disorder Chart pg 221-222) • Requires patients to be highly motivated and adherent, and able to follow up frequently.[18] Perhaps better suited for those who have used opioids for a short duration.[7] • Injectable naltrexone is superior to oral naltrexone, and is considered similar in efficacy to bup-nal.[17]	**CI**: Acute hepatitis, liver failure, current opioid use **AE**: Nausea, headache, dizziness, vomiting, insomnia, rash, muscle cramps, depression. Injection specific AE: Injection site rxn (IM), GI perforation (Health Canada warning) **DI**: Opioids (must be opioid free ≥7 days, 10 days methadone) **M**: LFTs, regular urine drug screens	**Initial**: 25mg po once daily x 3 days **Maintenance**: 50mg po once daily. Alternative 3x weekly dosing of 100mg, 100mg, and 150mg. **Maximum**: 150mg po daily IM: 380mg Q4W (Gluteal)	$168
ADJUNCT AGENTS: α_2 adrenergic agonists bind to receptor to reduce noradrenergic hyperactivity, thereby decreasing withdrawal symptom intensity. NOT recommended as first line therapy when buprenorphine and methadone are available to patient.[8] Clonidine and lofexidine have the most evidence of the below agents.				
Clonidine **CATAPRES**, g 0.025▼, 0.1, 0.2 mg tab **Guanfacine** ✗ ⊗ **INTUNIV XR** 1, 2, 3, 4 mg tablets **Lofexidine** US, UK only **LUCEMYRA** 0.18mg tablet	• Compared to placebo, α_2 adrenergic agonists resulted in less severe symptoms of withdrawal (e.g. insomnia, muscle aches, distress and cravings)[18], longer times in treatment, and higher rates of treatment completion.[8] It also has some, but less abuse potential. • Three systemic reviews found the severity of withdrawal and treatment completion to be similar between α_2 adrenergic agonists, but worse than bup-nal.[8] • Though limited, evidence suggests clonidine and lofexidine are equally effective on withdrawal symptoms, with lofexidine having a superior adverse event profile,[8] including less effects on blood pressure.[19] • One study comparing naltrexone +/- guanfacine found that there was no difference in relapse rates, however the guanfacine group had lower perceived stress scores.[8] • Can be considered as **second line** if using opioid substitution is not possible.[8] • Should not be used in combination with methadone or buprenorphine except in cases of marked hypertension.[8] α_2 adrenergic receptor function is down-regulated in opioid dependence.[18]		0.1-0.2mg po Q4H (up to 1mg/day) x 7-14 days. Gradually taper by 0.2mg/day 1-2mg po daily for up to 14 days 0.54mg (three 0.18mg tablets) po QID for up to 14 days.[10]	$17-32 $56-66
Kratom: Made from preparations of *Mitragyna speciosa* tree, Kratom is touted as an opioid replacement, and analgesic and an anxiolytic.[19] Associated with potential dependence, similar to opioids. It has similar side effects (including respiratory depression) and has been linked to seizures, liver damage, and withdrawal.[19] Purity and contaminants, such as fentanyl and its synthetic derivatives, present an additional concern.[19]				

OAT Education Resources / Courses
Opioid Dependence Treatment Core Course (CAMH)
http://www.camh.ca/en/education/about/AZCourses/Pages/odtcore_odt.aspx
Buprenorphine-Assisted Treatment of Opioid Dependence: An Online Course for Front-Line Clinicians
http://www.camh.ca/en/education/about/AZCourses/Pages/BUP.aspx
MacHealth Opioids Clinical Primer
https://machealth.ca/programs/opioids_clinical_primer/
Suboxone Online Education Program: www.suboxonecme.ca
Opioid Agonist Therapy: Information for Clients (CAMH)
https://www.camh.ca/-/media/files/oat-info-for-clients.pdf
Starting Buprenorphine Therapy: A Guide for Patients (Womens College Hospital, Toronto)
https://www.womenscollegehospital.ca/assets/pdf/MetaPhi/Buprenorphine%20book%2018.01.05.pdf

Screening Tools (Many others available through opioidrisk.com)
Opioid Misuse Screening Tools for Chronic Pain Patients
http://mytopcare.org/wp-content/uploads/2013/05/COMM.pdf
COWS: http://www.metaphi.ca/assets/documents/provider tools/Scale_COWS.pdf
SOWS: http://www.rxfiles.ca.shal.idm.oclc.org/rxfiles/uploads/documents/Opioid-Tapering-Newsletter-Compilation.pdf
Methadone and Suboxone Prescribing Requirements
https://www.cps.sk.ca/imis/CPSS/Legislation_ByLaws_Policies_and_Guidelines/Legislation_Content/Policies_and_Guidelines_Content/Methadone_Prescribing.aspx
https://www.cps.sk.ca/imis/CPSS/Programs_and_Services/Methadone_Program_Overview.aspx?MethadoneCCO=Methadone%20Program%20Overview
Buprenorphine/Naloxone Guide – Hosted Link for Simplified Info from Alberta Pharmacists
https://www.rxfiles.ca/RxFiles/uploads/documents/CHT-OUD-BupNx-Guide-Alberta.pdf

Switching Between Suboxone and Methadone
Refer to Appendices 1 & 2 in BC Provincial OUD Guideline http://www.bccsu.ca/wp-content/uploads/2017/06/BC-OUD-Guidelines_June2017.pdf
AFP – OUD Medical Tx Options: https://www.aafp.org/afp/2019/1001/p416.html
CFP – OUD in Primary Care: https://www.cfp.ca/content/65/5/321.long
Cultural Safety Resources
Saskatchewan: https://www.usask.ca/cmelearning/online-learning/indigenous-wellness.php#CourseContent
BC: http://www.sanyas.ca/
Trauma Informed Practice: http://bccewh.bc.ca/wp-content/uploads/2012/05/2013_TIP-Guide.pdf
Trauma Informed Practice power point available from
http://www.metaphi.ca/provider-education.html

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See also related resources at www.RxFiles.ca:

- **RxFiles Pain Mini Book**
- **Substance Use Disorder / Addiction: Overview and Considerations Chart**
- **Stimulant Use Disorders Chart**
- **RxFiles Opioid and Pain Related Links**

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Who could be a candidate for cannabinoid therapy?

- Cannabinoids are generally not considered first- or second-line therapy for any indication. Reserve use for patients who have failed other therapies.[2] Conduct a trial over 4-12 wks; review benefit vs harm
  e.g. may consider if tried ≥3 drugs for neuropathic pain or ≥2 drugs for palliative pain or if refractory to standard therapies for CINV, spasticity in MS or SCI, or cachexia [or refractory pediatric seizure]
- Watch for relative **contraindications** such as **pregnancy**, **breastfeeding**, age <21-**25**, a history of psychosis/schizophrenia, or substance abuse history. For more details, see RxFiles Cannabis Q and A.

Prescribing/Authorizing Cannabinoids Safely

Cannabinoids are potential drugs of abuse; caution is needed when prescribing. In general, follow similar principles to prescribing opioids (see page 131-132). A summary of these principles is as follows:

- ☐ Optimize suitable non-cannabis therapies first (drug and non-drug)
- ☐ Check Prescription Drug Monitoring Programs (e.g. PIP in SK) at baseline & at each visit
  These programs do not record medical cannabis. Option to check order hx with Licensed Producer.
  Document cannabis use on local EMR (just like tobacco, alcohol, etc.).
- ☐ Baseline urine drug screen, and randomly thereafter
  THC metabolite detected = THC-COOH. Note: urine drug screens in SK do not test for CBD.
- ☐ Assess risk of addiction, and monitor for cannabis use disorder →
- ☐ Ensure the patient understands cannabinoids are prescribed as a **trial**
  Reasonable trial duration may be ~12 weeks.
- ☐ Obtain Treatment Agreement and Informed Consent
  Search "agreement" at www.rxfiles.ca for a sample cannabinoid tx agreement.
  Agreement includes safe storage – especially important if kids nearby![67]
- ☐ Monitor for benefits & harms. **Exit Strategy**: stop (often taper) if trial unsuccessful.
  Possible taper to prevent withdrawal: ↓ by 25% q1week.
  Monitor more vigilantly in those at higher risk, esp where quality evidence/guidelines lacking.

Monitoring for Cannabis Use Disorder (CUD)

9% of adults who use cannabis non-medically may develop addiction (& up to 17% if started in adolescence).[51,76,77]

Prior to Tx: Screen for CUD

1) Options for Screening:

CUDIT-R
specific to cannabis.[45]

CAGE-AID Questionnaire
short & practical.[46]

2) Diagnosing:
use DSM-5 criteria.[53] Link
-11 components, 2 or more +'ve

{**4Cs of Addiction**: Craving, loss of Control, Compulsive use, Continued use despite harm}

During Tx: Monitor for CUD

- rapid or unsanctioned dose ↑
- frequent changes needed
- wants dried cannabis only
- wants high potency THC only
- misuse of other substances
- urine drug screen: aberrant
- concerns from friends/family
- poor functioning (school/work/social)
- missed follow-up; reports of lost or stolen cannabis

In primary care,[47] watch for:

- ♦respiratory problems
- ♦depression/anxiety/amotivation
- ♦issues functioning/concentrating (e.g. in studies, work, relationships)
- ♦those at ↑risk of self-injury/harm (e.g. veterans - suicidality, seniors - AEs, DIs)

Treating CUD:[48-50]

a) Brief interventions
b) Withdrawal management
(e.g. sleep hygiene, brief symptomatic relief, ?nicotine replacement)
c) Psychosocial interventions
(e.g. motivational enhancement, CBT)

[Note: Pharmacologic tx, e.g. naltrexone, appears ineffective at this time] Cochrane'19

Symptoms of Cannabis Withdrawal (onset 1-2 days, peak 2-6 days)

Anger, aggression, appetite change, weight loss, **anxiety**, irritability, restlessness, sleep disturbance, cannabis craving, physical discomfort.

Choosing Between Products

note: currently Canada has a "two-stream" cannabis system: medically authorized cannabis, and cannabis through retail sale.

	Prescription Cannabinoids e.g. nabilone, nabiximols	Cannabis	
		via medical authorization	via retail sale
Quality Control	Regulated. Health Canada pharmaceutical production standards in place (has Drug Identification Number).	In Saskatchewan, sellers from both medical & retail streams use the same cannabis sources (a Health Canada licensed producer). Production standards exist, including testing for pesticides & THC/CBD concentrations.[43] However, similar to non-Rx herbal supplements, cannabis may have less vigorous production standards than Rx drugs.	
Dosing & Guidance	• Standardized. • Some indications and dosing are Health Canada approved. • Will show up on the electronic medical record (e.g. PIP in Saskatchewan).	• Challenging. e.g. THC in 1 puff of cannabis joint can range from 1 to >10mg. No "studied usual dose". • Prescriber may pick strain/ratio and max quantity allowed for patient. May limit duration, e.g. "one 60mL bottle of CBD oil, then see prescriber for further authorization." • Overall, less control than prescription products (e.g. "dosing interval" does not exist).	Patient selects the product, dose, dosing interval, and route of administration. Difficult to provide monitoring, boundaries, or education.
	Note: despite prescriber attempts to guide product and dosing, patients may supplement with retail cannabis against medical advice.		
Access	Dispensed by community pharmacy.	Exclusively by mail/courier.	At cannabis retail store; online ordering possible too.
Paperwork	Written or electronic prescription.	See **Paperwork Required for Medical Cannabis** box, right.	None.
Coverage	• Occasional private insurance coverage. • SK EDS and prior approval criteria for specific indications.	• Occasional private insurance coverage (e.g. Manulife and Sunlife on a case-by-case basis as of 2018). • Veteran's affairs coverage (max 3g/day dried cannabis)	No coverage by any drug plans or private insurance; can't be claimed on income tax.
		~$8/gram; May grow at home to ↓costs. {Calculator for home production limit amount - link below}	Average price still uncertain (Ranges from $8-20/gram)

Paperwork Required for Medical Cannabis

1. Complete medical document form (link ❶). In SK, complete treatment agreement form (link ❷, or visit RxFiles.ca and search "agreement").[56]
2. Submit medical document to Licensed Producer (link ❸) who mails cannabis (dried, oil, buds, or leaves) to patient.
3. **Or**, patients may apply to grow their own product at home (e.g. 15 plants for 3g/day, see link ❹).
4. Medical document must be re-authorized at least once per year.
5. In SK, prescribers required to keep list of pts.
6. No set daily limit; max possession is lesser of 150g or 30 times daily amount.

❶ www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/info/med-eng.pdf
❷ http://www.cps.sk.ca/iMIS/Documents/Programs%20and%20Services/Patient%20Agreement%20Template%20-%20Medical%20Cannabis.pdf
❸ www.hc-sc.gc.ca/dhp-mps/marihuana/info/list-eng.php
❹ www.canada.ca/en/health-canada/topics/production-cannabis-for-your-own-medical-purposes.html

Medical users (vs recreational):
- Use more frequently
- Use products other than dried flower & trend towards low THC/high CBD

Calculator for the production of a limited amount of cannabis for medical purposes: http://health.canada.ca/en/health-canada/services/drug-health-products/buying-using-drug-health-products-safely/cannabis-medical-purposes/accessing-cannabis-medical-purposes/production-cannabis-medical-purposes/calculator.html

☎=EDS in SK ✆=prior approval NIHB ✗ =not covered SK ⊗=not covered NIHB ⌂=NIHB palliative care **2-AG**=2-Arachidonoylglycerol **AEA**=Anandamide **CBD**=cannabidiol **CB1**=cannabinoid receptor type 1 **CB2**=cannabinoid receptor type 2 **CBZ**=carbamazepine **CINV**=chemotherapy-induced nausea and vomiting **CUD**=cannabis use disorder **MS**=multiple sclerosis **PIP**=pharmaceutical information program **TCA**=tricyclic antidepressant **SCI**=spinal cord injury **SJW**=St. John's Wort **THC**=delta-9-tetrahydrocannabinol

College of Physicians & Surgeons of Saskatchewan: The College's bylaw

The College's bylaw which regulates physician authorization of medical marihuana is now in effect. The bylaw is numbered Bylaw 19.2 of the regulatory bylaws of the College and is available at the College's website. Visit: http://www.cps.sk.ca/imis/CPSS/CPSS/Programs_and_Services/Medical_Marijuana/Medical_Cannabis.aspx. 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

Sample treatment agreement: http://www.cps.sk.ca/iMIS/Documents/Programs%20and%20Services/Patient%20Agreement%20Template%20-%20Medical%20Cannabis.pdf

Or visit www.RxFiles.ca and search "agreement".

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.

Submitting Adverse Effect information to Health Canada:
https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/recalls-adverse-reactions-reporting/report-side-effects-cannabis-products.html

Tips on filling out Part D (for cannabis products i.e. dried cannabis or cannabis oils)

- DIN or NPN is not required
- Include: brand name, strain name, lot #, licensed holder name, intended use (medical or non-medical)
- If the product was not purchased from a legal retailer it can still be reported but it would be useful to indicate if it was purchased from a non legal source so it can be processed properly in our database.

Cannabinoid	**139**
Cannabinoid Use Disorder	139
Cannabis	**139**
CBD	**139**
Marijuana	139
Medical Cannabis	139
Anorexia	140
Cannabidiol	140
Cannabinoid	**140**
Cannabis	**140**
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Dried Cannabis	140
Dronabinol	140
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MARINOL	140
Nabilone	**140**
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SATIVEX	140
Smoked/vapourized Cannabis	140
Tetranabinex/nabidiolex	140
THC	140

References: Cannabinoid Chart – www.RxFiles.ca

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ACUTE PAIN MANAGEMENT FOR PEOPLE ON CHRONIC OPIOIDS/OPIOID AGONIST THERAPY

A Wiebe BSP, A Crawley © www.RxFiles.ca Mar 2021

Concerns about Problematic Chronic Opioid Use:

- If concerned about problematic opioid use by people on opioids chronically for pain, assess for OUD (see RxFiles: Concomitant Chronic Pain and Opioid Use Concerns chart).
- Avoid stigmatizing people on chronic opioids by undervaluing their expression of pain &/or placing labels such as "drug-seeking." Pre-existing tolerance may mean using higher than usual opioid doses for analgesia.

Considerations Specific to Acute Pain for People with Opioid Use Disorder (OUD):

For patients with OUD & acute pain who are on OAT: Maintain OAT in most cases. The risks of changing (lowering or stopping) OAT **can lead to dangerous outcomes** & generally outweigh benefit.

Risks can include:[7]

- destabilization & return to use (i.e. relapse).
- unintentional **overdose & death** (resulting from return to use after loss of tolerance).
- ↑ patient anxiety, ↓ trust/loss of therapeutic alliance.
- dose conversion challenges (e.g. medication errors).
- ↑ pain & other opioid requirements.
- challenges restarting (e.g. loss to follow-up, overlooked/lack of community coordination at discharge, precipitated withdrawal[if bup stopped then restarted]).[6]

If additional opioids are indicated, hydromorphone po/IV (or fentanyl IV[caution]) may be preferred while on bup due to its potency & ↑ mu-receptor affinity. Discussion with the patient may identify specific opioids they wish to avoid (e.g. due to their concerns about the prior opioid of use & potential for relapse).

For patients with OUD & acute pain who are interested in starting OAT: Offer OAT concurrently. Methadone may be preferred if severe pain with use of concurrent opioids,[8,9] though some clinicians initiate bup-nal using a microdosing[32] approach to target bup 8-12mg while using concurrent IR opioids during the acute pain episode[(expert opinion)]. If delaying the start of OAT, plan to initiate immediately after acute pain resolved (bup-nal preferred when other opioids are no longer indicated and have been discontinued).

For patients with OUD & acute pain who are not currently interested in starting OAT: Goals are to reduce acute pain (optimize non-opioid analgesics & non-pharm strategies), minimize harms, alleviate opioid withdrawal, & establish therapeutic relationship.

In most cases:	If managing as an outpatient:	If managing as an inpatient:
• Confirmatory UDS. • Offer take home naloxone kit & other harm reduction options. • Consider screening for HIV, Hep B/C, STIs, pregnancy as appropriate.	• Communicate concern about OUD alongside open offer to discuss OAT options. • Consider short structured opioid course (e.g. daily dispensing) with sunset clause based on expected duration of severe pain (consult with primary provider).	• Assess withdrawal (monitor COWS, baseline & often q4hr while awake until score consistently ≤12). • Estimate & replace baseline opioid reqs to treat withdrawal symptoms & pain (IV may be preferred for ease of administration/ comfort/titration if IV access & pt was using IV as outpt[expert opinion]). • Offer concurrent pharmacological opioid withdrawal adjuncts (e.g. clonidine, loperamide, NSAIDs, dimenhydrinate, hydroxyzine).

Considerations Specific to Acute Pain in the Emergency Department/Acute Care Settings:

- People using opioids chronically may need to be admitted for pain control for procedures that would otherwise be tolerated as outpts for those not on chronic opioids.
- If patient with untreated OUD admitted, treat acute pain & withdrawal concurrently (monitor COWS). Offer OAT. Generally, prefer methadone if not planning to continue as outpatient.[8,9] Consult pain/addiction medicine specialist PRN.
- When possible, involve the patient & their primary prescriber in making a clear, proactive plan for structure, support, & opioid discontinuation.
- Be aware of treatment agreement in place with other prescribers. If opioids used, this should be communicated to the primary prescriber.
- Conduct a pre-procedural assessment when possible to assess risk of postoperative increases in pain/persistent opioid use,[11] & risk of respiratory depression / overdose / peri-operative complications (e.g. screen for OSA) as well as to establish early recovery after surgery protocols.
- Consider using the **Clinically Aligned Pain Assessment (CAPA) Tool**[20] to ask about: comfort, change in pain severity, pain control, functioning, & sleep.

Medication History:

- Communication with community pharmacist is helpful to confirm med hx (verify if patient receives daily dispensed/directly observed therapy or take home doses), as well as to ↓ risk of diversion (medications may be dispensed to patient/others while hospitalized & receiving doses as an inpatient).
- Be aware of & continue prior subcutaneous, trans- & intra-dermal formulations of buprenorphine the patient has been prescribed.
- If CNS/resp depression occurs when given opioid equivalent to "home doses," consider potential for 1) outpt diversion, 2) outpt non-adherence, 3) concurrent illness (e.g. infection, AKI, brain injury), &/or 4) medications (e.g. alcohol, BZD, other sedatives) decreasing opioid requirements/increasing adverse effects.
- Reversal of buprenorphine overdose may require ↑ naloxone doses (e.g. 2mg IM/IV q2-3min PRN) relative to other opioids.

Adjunctive Agents & Additional Opioids:

- Consider use of adjuncts unique to acute care/supervised settings: single dose corticosteroids (e.g. methylprednisolone, dexamethasone), NMDA antagonists (e.g. ketamine, nitrous oxide), alpha-2 agonists (e.g. dexmedetomidine, clonidine), IV lidocaine. Utilize regional and neuraxial anesthesia to minimize other pharmacotherapies, if available & appropriate.
- If additional opioid deemed necessary for a patient on high potency chronic opioids/OAT, likely will need 2nd structured opioid regimen with higher & more frequent dosing to overcome receptor affinity & tolerance.[1,8] Consider additional bowel care as warranted.
- Oral routes generally preferred to IV for post-operative analgesia whenever possible.[24] However, note conditions that affect GI function/warrant NPO. Switch to most equivalent baseline opioid dose if prior dosage form not feasible (e.g. change from po because IV required). If switching to a different opioid, ↓ dose (e.g. by 25-50%) for incomplete cross-tolerance.
- Offer PCA (bolus only, once initial dose determined) if available for severe pain → provides sense of control. Reassess pain control/dose frequently. Transition to equivalent po dosing (if this was the route taken prior to admission) as soon as able.
- Parenteral fentanyl can be a short-term option for severe/incident pain (in closely monitored settings) due to potency & quick onset/offset (parenteral formulation may also be administered SL).
- Use caution when calculating doses to switch back to home regimen from parenteral dosing. Often start with scheduled doses, though may encourage patient to refuse doses that are above the baseline opioid requirements if analgesia is sufficient (reminder: avoid causing opioid deficit). Adjust subsequent dose/interval accordingly.[17]

Discharge Planning:

- Determine Rx at discharge based on prior 24hr requirements (no Rx if not used in 24hrs). Consider patient's ability to attend follow-up appointments and pharmacy access. Coordinate with community prescriber and pharmacist. Ensure patient has access to take home naloxone.

"What happens if I have acute pain while on bup-nal?" – addressing patient concerns

Acknowledge concern:

- Other opioids may not work as well for pain when taking higher doses of bup-nal (e.g. >12mg).

Offer reassurance:

- We have evidence that in many cases, an anti-inflammatory +/- acetaminophen work just as well, if not better, than opioids for mild to moderate pain. This means most pain can be well managed with non-opioid medications & strategies.
- When severe pain does occur, in most cases the bup-nal can be continued at the same dose & the pain can be treated with other opioids layered on top for a short time. This may require using higher than usual opioid doses.

Recognize choice:

- There are options for how to approach the acute pain episode, especially for planned procedures where severe pain is anticipated.
- Though stopping the bup-nal during an acute pain episode is generally discouraged, we could consider temporarily adjusting the dose to help with the pain. This might include lowering, increasing or splitting the dose for a brief period of time.

Offer & invite collaboration:

- Encourage the patient to discuss any questions or concerns they have about their pain management, breaking a treatment agreement, or returning to use (i.e. relapse).
- Invite patients to proactively create pain & relapse contingency plans together with their care providers.

AKI=acute kidney injury **bup**=buprenorphine **BZD**=benzodiazepines **CABG**=coronary artery bypass graft **CDN**=Canadian **CI**=contraindicated **CNCP**=chronic non-cancer pain **CNS**=central nervous system **COX-2**=selective cyclooxygenase inhibitor **d**=day **def**=deficiency **ER**=emergency room **esp**=especially **FDA**=approved Food & Drug Admin. **HA**=headache **hx**=history **inpt**=inpatient **IR**=immediate release **IV**=intravenous **LBP**=low back pain **MED**=morphine equivalent dose **mos**=months **nal**=naloxone **NMDA**=N-methyl-D-aspartate

ACUTE PAIN MANAGEMENT FOR PEOPLE ON CHRONIC OPIOIDS/OPIOID AGONIST THERAPY

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

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

About 90% of patients with acute low back problems spontaneously recover activity tolerance within 4 weeks. 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.

****

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

Red Flag acronym NIFTI:	
N=	Neurological
I =	Infection
F =	Fracture
T =	Tumor
I =	Inflammation

Link to CEP Back Pain Tools: https://thewellhealth.ca/low-back-pain/
Link to BMJ LBP & Sciatica Visual Summary:
https://www.bmj.com/content/bmj/suppl/2017/01/06/bmj.i6748.DC1/beri151216.w1.pdf

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.

Cannabinoids – acute pain:

- Harm likely to outweigh benefit. Lack of evidence for benefit.
- CFP 2018 Guidelines for Cannabinoids strongly recommend against use in acute pain.

Link to Dalhousie Academic Detailing - Acute Pain Resource: https://cdn.dal.ca/content/dam/dalhousie/pdf/faculty/medicine/departments/core-units/cpd/academic-detailing/AcutePainHandout2021.pdf

See also Chronic Pain chart – pg 127; **Back Facts (** 10 facts every person should know (BMJ) https://bjsm.bmj.com/content/early/2019/12/31/bjsports-2019-101611

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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

GOUT: Online Extras

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Gout Diet based on RCTs [ACR 2012]

ENCOURAGE
- Low-fat or non-fat dairy products; vegetables; adequate hydration.

LIMIT
- Serving sizes of beef, lamb, pork, & seafood with high purine content (e.g. sardines, shellfish).
- Servings of naturally sweet fruit juices, table sugar, sweetened beverages, and desserts.
- Table salt, including in sauces and gravies.

AVOID
- Organ meats high in purine content (e.g. sweetbreads, liver, kidney).
- High fructose corn syrup-sweeted sodas, other beverages, or foods.[31]
- Alcohol overuse (>2 servings/day for males and >1 serving per day for females). Avoid alcohol completely during gout attacks or when gout is poorly controlled.

Useful Links
CDC http://www.cdc.gov/arthritis/basics/gout.htm
American College of Rheumatology: Gout www.rheumatology.org/public/factsheets/diseases_and_conditions/gout.asp?aud=pat
Arthritis Foundation: Gout www.arthritis.org/disease-center.php?disease_id=42
National Institute of Arthritis and Musculoskeletal and Skin Diseases: Questions and Answers About Gout www.niams.nih.gov/Health_Info/Gout/default.asp
Gout and Uric Acid Education Society www.gouteducation.org/

Additional Pharmacologic Agents

Generic/TRADE	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	Dosing	$/30d
ACETAMINOPHEN: Analgesic. Can help with gout-associated pain, but will not resolve a gout flare. Potentially useful in combination with corticosteroids.			
Acetaminophen TYLENOL, g OTC 325,500,650mg tab ▼ ✗ PL	• **AE**: **Common**: rash, GI upset. **Serious**: hepatotoxicity. **Precautions**: Liver dysfx &/or alcoholism • **DI**: Warfarin (at doses 2000mg/day or higher) • **M**: Liver function tests if long term & ↑EtOH intake	650-1000mg po q6h (prn; adjunct to CS) Max 4000mg/d	15-25
URICOSURICS: ↑uric acid excretion. Drink 2 liters of water per day to improve excretion and prevent nephrolithiasis. Do not initiate during an acute gout flare. Consider gout flare prophylaxis when initiating therapy.			
Probenacid BENURYL, g 500mg tab Gentes & Bolduc Pharmaciens; SAP	Typically trial a second xanthine oxidase inhibitor prior to using a uricosuric.[ACR 2020] • **AE**: rash, GI upset, headache. Serious: allergic reactions, blood dyscrasias. • **CI**: blood dyscrasias; nephrolithiasis hx; G6PD deficiency; **ineffective if CrCl<30-50**mL/min • **DI**: ASA ↓effect of probenacid. ↑levels of penicillins/cephalosporins (can be used to prolong dosing interval), MTX, NSAIDs, theophylline.	Usual: 1000mg BID Range: 500-2000mg / day	34
Sulfinpyrazone ANTURAN, g 200mg tab	• **AE**: GI upset, GI bleed, skin rash. Serious: blood dyscrasias. • **CI**: active peptic ulcer, severe hepatic or renal disease • **DI**: ASA ↑toxicity. Has antiplatelet effect - ?benefit in cardiovascular disease.	Usual: 100-200mg BID with food	17-27
Benzbromarone special access CDN [30]	• **AE**: diarrhea. **Rare**: hepatotoxicity, rash, impotence, allergic conjunctivitis. • **DI**: ↓effect of benzbromarone: ASA, sulfinpyrazone; ↑levels: warfarin. • **M**: LFTs.	Initiate: 25mg po daily Usual dose: 100mg daily OK in renal dysfunction as low as 20mL/min	
URATE OXIDASE ENZYME: This enzyme is present in animals other than humans; it further metabolizes uric acid into inactive allantoin, which can then be excreted more readily than uric acid.			
Pegloticase KRYSTEXXA USA 8mg vial for injection	Do not use pegloticase in mild gout, and only use 3rd line after xanthine oxidase inhibitors, uricosurics, and other interventions have failed to control severe gout.[ACR 2020] Commonly (up to 74% of patients) will result in gout flare upon initiation; start prophylaxis first and continue for up to six months. • **AE**: nausea 12%, bruising 11%, injection site reactions 26%. **Serious**: allergic reactions 7%. • **CI**: G6PD, ↑↑sUA levels, may exacerbate heart failure. • **DI**: Not for concurrent use with other uric acid lowering therapies (e.g. allopurinol, febuxostat, probenacid) as may increase risk of allergic reaction.	8mg via IV over ≥2hr q2-4 weeks	2000
Rasburicase FASURTEC 1.5, 7.5mg vial for injection	✓ Indicated for hyperuricemia associated with **malignancy** (i.e. symptoms from cancer tumor lysis) in adults or kids of any age. • **AE**: peripheral edema 50%, rash 13%, GI upset 50%, fever 46%. **Serious**: allergic reactions 4%, methemoglobinemia. • **CI**: G6PD deficiency. **DI**: none known. • **M**: sUA levels, CBC, signs of hypersensitivity. Onset within 4 hours.	0.2mg/kg IV once daily for 5-7 days along with concurrent hyperuricemia-inducing chemotherapy. May use standard dose of 3mg in adults. Only indicated for ONE treatment course (?rapid resistance)	1000 to 4000

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Generic/TRADE	Comments	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitoring M	Initial, Usual & Maximum Dose	$/year
Etidronate (Eti) x▼ DIDRONEL,g D/C 200mg tab DIDROCAL KIT, g 14 x Etidronate 400mg white,♀ PLUS 76 Calcium Carbonate blue 1250mg (500mg elemental Ca^{2+})	Etidronate is a **weak antiresorptive** agent & may be effective in ↓risk of vertebral # in those at high risk. (not ↓ hip or non-vertebral #'s) ↓cost, but ↓#evidence. Not approved by FDA for prevention # or OP tx.	**Common** vs pl: **GI AE**: (diarrhea 37 vs 31%, dyspepsia 12 vs 11%, flatulence 17 vs 15%, nausea 18 vs 14%), dizzy 16 vs 11%, headache 2% **Serious (rare)**: arthropathy (arthralgia, arthritis), ocular disorders, esophagitis, glossitis, angioedema, skin rashes, pruritus, Stevens-Johnson syndrome, urticaria, osteomalacia, leukopenia 1/100,000, agranulocytosis, pancytopenia **CI**:: Overt osteomalacia, **esophageal** abnormalities: Barrett's, delayed emptying stricture, achalasia, low Ca^{++} **DI**: Food/Ca^{2+}/Iron/Mg^{2+} may ↓ absorption of etidronate; warfarin ↑INR reports, Ca^{2+} may ↓ absorption of: cipro, HIV PI, iron, tetracycline, levothyroxine. Etidronate on an **empty stomach**, with a full glass of water at **bedtime**, at least **2 hrs before or after** eating. Take calcium with food.	Etidronate 400mg hs x 14 d, then calcium 500mg daily x 76days ⇒ cycle therapy. {**Continuous** eti can impair mineralization of the bone}	**128 g**, (237 Trade) {Full formulary} SPDP&NIHB

Drug Induced OP: ↑ alcohol, antacids aluminum, anticonvulsants CBZ, phenobarbital, phenytoin, primidone, apalutamide, aromatase inhibitors anastrozole, letrozole, exemestane, canagliflozin (other SGLT2 inhibitors?), **glucocorticoids** >3 months (oral or inhaled corticosteroids in asthma patients, high dose topical corticosteroids), hypogonadism drugs causing: parenteral progesterone, gonadotropin-releasing hormone agonists (LHRH, GnRH), heparin if Tx > 30day, **immunosuppressants** cyclosporine, tacrolimus, lithium, medroxyprogesterone >2yr tx, methotrexate, proton pump inhibitors, smoking, SSRIs, tenofovir, ↓testosterone in ♂, thiazolidinediones pio- & rosi-glitazone, thyroid hormone excess & Vit A ↑ dose.

Investigational SERMS: **Lasofoxifene**: 0.25-0.5mg PEARL daily **AE**: ↑VTE but may ↓breast cancer.
Other: **Chlorthalidone** thiazides associated with ↓hip/pelvic #'s. ALLHAT
Not CDN: **Strontium** ranelate **PROTELOS**-2g hs, diarrhea, seizure, rash DRESS sx, VTE , ↑MI TROPOS. **Ibandronate BONIVA** 2.5mg tab OD, 60min before first food, 150mg tab po monthly; 3mg IV q3mos.

Risk Factors for Atypical Femur Fractures: Asian, bisphosphonate use > 3 years, glucocorticoid use ≥ 1 year

Incidence of atypical femor fractures and estimate of fractures prevented Black et al, NEJM'20

	3 years		5 years		10 years	
Women	White ♀	Asian ♀	White ♀	Asian ♀	White ♀	Asian ♀
Clinical fractures prevented	541	330	859	524	1363	831
Hip fractures prevented	149	91	286	174	591	360
Atypical femoral fractures	2	8	8	38	38	236

Data are fractures/10,000 women, presented according to the number of years of bisphosphonate treatment.

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Bisphosphonate	**145**
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Alendronate	**146**
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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

Updated 2010, but tables initially in Can Assoc Radiol J 56, Siminoski K et al, Recommendations for Bone Mineral Density Testing in Canada, p. 178-188, Copyright Canadian Association of Radiologists 2005

FORE (Foundation for Osteoprosis Research & Education) 10 year fracture risk calculator https://riskcalculator.fore.org/

- Includes spine T-score.
- Steroid use has a greater impact on spine BMD. For steroid treated patients with discordant spine and hip BMD (i.e., lower spine BMD), this risk calculator is available.

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FDA Oct/10 **Atypical subtrochanteric femur fractures** are fractures in the bone just below the hip joint. Diaphyseal femur fractures occur in the long part of the thigh bone. These fractures are very uncommon and appear to account for less than 1% of all hip and femur fractures overall. Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates.
FDA Nov/10 has approved **denosumab** (marketed as **Xgeva**) for the prevention of fracture and bone pain in patients with cancer that has metastasized to the bone. FDA news release (Free) Xgeva prescribing information (Free PDF)
FDA July/11 notified healthcare professionals and patients about its ongoing review of data from published studies to evaluate whether use of **oral bisphosphonate** drugs is associated with an **increased risk of cancer of the esophagus**. FDA has not concluded that taking an oral bisphosphonate drug increases the risk of esophageal cancer. There are insufficient data to recommend endoscopic screening of asymptomatic patients.
FDA Sep/11 notified healthcare professionals and patients of an update to the drug label for **Reclast (zoledronic acid)** regarding the risk of kidney failure. Cases of acute renal failure requiring dialysis or having a fatal outcome following Reclast use have been reported to FDA. The revised label states that Reclast is contraindicated in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment.
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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**.
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Moderate-quality evidence suggests that tibolone is more effective than placebo but less effective than HT in reducing menopausal vasomotor symptoms, and that tibolone is associated with a higher rate of unscheduled bleeding than placebo but with a lower rate than HT.Compared with placebo, tibolone increases recurrent breast cancer rates in women with a history of breast cancer, and may increase stroke rates in women over 60 years of age. No evidence indicates that tibolone increases the risk of other long-term adverse events, or that it differs from HT with respect to long-term safety.Much of the evidence was of low or very low quality. Limitations included high risk of bias and imprecision. Most studies were financed by drug manufacturers or failed to disclose their funding source.
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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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superiority of any specific aminobisphosphonate (zoledronate, pamidronate or ibandronate) or nonaminobisphosphonate (etidronate or clodronate) for any outcome. However, zoledronate appears to be superior to placebo and etidronate in improving overall survival.

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]

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PEDIATRIC PAIN: Online 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

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

- **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.uhealthcare.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/ ; **Clinic**:https://momsandkidssask.saskhealthauthority.ca/infant-child-health/specialty-care/pain-clinic
- **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/00428_Short-Acting-Procedural-Sedation_to_e.pdf

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Pain Intensity Scoring:

- Chose a scale that is age appropriate to patient & become familiar with using!
- Interpret in light of any other pain related physical factors (e.g. heart rate)
- Also interpret according to trends for improvement or worsening of pain control
- Sherbrooke algorithm for acute pain in children (post-op): gave regular analgesic according to pain scale: {0-3: acetaminophen; 3-6: naproxen + acetaminophen; 6-9: morphine + naproxen + acetaminophen; 9-10: notify MD. Overall ↓ in pain scores & a ↓ in opioid requirement as algorithm required patient to receive round the clock acetaminophen and NSAID if opioid recieved.}
- Other links: **Visual Analogue Scale**: suitable for age 7+ {McGrath PA, Seifert CE, Speechley KN, et al. A new analogue scale for assessing children's pain: an initial validation study. Pain. 1996 Mar;64(3):435-43.} **Oucher Scale**: age 3-12: http://www.oucher.org/history.html

FLACC SCALE – for assessing 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,	Difficult to console or

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.

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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Vaccination & antipyretic interactions [Wysocki 2017]**:**

- Acetaminophen may interfere with pneumococcal vaccinations
- Ibuprofen may interfere with pertussis and tetanus vaccinations

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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
FDA May/18 is warning that over-the-counter (OTC) oral drug products containing benzocaine should not be used to treat infants and children younger than 2 years. We are also warning that benzocaine oral drug products should only be used in adults and children 2 years and older if they contain certain warnings on the drug label. These products carry serious risks and provide little to no benefits for treating oral pain, including sore gums in infants due to teething. Benzocaine, a local anesthetic, can cause a condition in which the amount of oxygen carried through the blood is greatly reduced. This condition, called methemoglobinemia, can be life-threatening and result in 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.
Health Canada Oct/20 is reminding parents and caregivers not to use products containing **benzocaine** in children under two years of age. Benzocaine products may cause a serious blood condition called methemoglobinemia (MetHb), which reduces the ability of red blood cells to deliver oxygen throughout the body.
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💻 Rheumatoid Arthritis: Online Extras

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ACR/EULAR 2010 RA scoring system for diagnosis of rheumatoid arthritis[48] see calculator at https://www.rheumakit.com/en/calculators/acr_eular2010

	Category	Points
Joint Involvement	1 large joint	0
	2-10 large joints	1
	1-3 small joints (with or without involvement of large joints)	2
	4-10 small joints (with or without involvement of large joints)	3
	>10 joints, including at least one small joint	5
Serology	Negative RF and negative ACPA	0
	Low positive RF or low positive ACPA	2
	High positive RF or high positive ACPA	3
Acute Phase Reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of Symptoms	< 6 weeks	0
	≥ 6 weeks	1
A total score of 6 or higher is indicative of rheumatoid arthritis.		

Sensitivity of the scoring system[68] (likelihood of correctly diagnosing a true case of rheumatoid arthritis): 82%
Specificity of the scoring system[68] (likelihood of correctly ruling out rheumatoid arthritis): 61%

Interesting note: for every 10km a patient lives away from a rheumatologist, the liklihood of being prescribed a biologic drops by 1%.[78]

Biologic	148
DMARD	148
Hydroxychloroquine	148
Leflunomide	148
Methotrexate	148
Rheumatoid Arthritis	148
Sulfasalazine	148
Abatacept	149
ACTEMRA	149
Adalimumab	149
AMJEVITA	149
Anakinra	149
AVSOLA	149
Baricitinib	149
Biologic	149
BRENZYS	149
Canakinumab	149
Certolizumab	149
CIMZIA	149
CYLTEZO	149
DMARD	149
ENBREL	149
ERELZI	149
Etanercept	149
Golimumab	149
HUMIRA	149
ILARIS	149

INFLECTRA	149
Infliximab	149
KEVZARA	149
KINERET	149
Malignancy	149
OLUMIANT	149
ORENCIA	149
REMICADE	149
RENFLEXIS	149
Rheumatoid Arthritis	149
RINVOQ	149
RITUXAN	149
Rituximab	149
RIXIMYO	149
RUXIENCE	149
Sarilumab	149
SIMPONI	149
Tocilizumab	149
Tofacitinib	149
TRUXIMA	149
Upadacitinib	149
XELJANZ	149
AMETHOPTERIN	150
ARAVA	150
Azathioprine	150
CUPRIMINE	150
Cyclosporine	150
DMARD	150
Gold	150
Hydroxychloroquine	150
IMURAN	150
Leflunomide	150
Methotrexate	150
MINOCIN	150
Minocycline	150
MYOCHRYSINE	150
NEORAL	150
Penicillamine	150
PLAQUENIL	150
Prednisone	150
PROGRAF	150
Rheumatoid Arthritis	150
RIDAURA	150
SALAZOPYRIN	150
Sodium Aurothiomalate	150
Sulfasalazine	150
Tacrolimus	150
HADLIMA	149
IDACIO	149
HULIO	149
HYRIMOZ	149

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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.
FDA Feb/19: **Xeljanz, Xeljanz XR** (tofacitinib): Safety Communication - Safety Trial Finds **Increased Risk of Blood Clots** in the Lungs and Death with Higher Dose in Rheumatoid Arthritis Patients.
FDA July/19: has approved new warnings about an increased risk of blood clots and of death with the 10 mg twice daily dose of **Xeljanz, Xeljanz XR (tofacitinib)**, which is used in patients with ulcerative colitis.
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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.
Health Canada Mar'19: Clinical trial finds an increased **risk of blood clots in the lungs and of death in rheumatoid arthritis patients taking high dose of tofacitinib** (sold as Xeljanz or Xeljanz XR)
Health Canada May/19: **ACTEMRA® (tocilizumab) – Risk of Hepatotoxicity** - Hoffmann-La Roche Limited, serious cases of drug-induced liver injuries (DILI) have been reported in patients treated with ACTEMRA, including cases of acute liver failure requiring a transplant.
Health Canada Nov/19: An increased incidence of thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, was observed in patients treated with **XELJANZ** in a large, ongoing post-marketing study.
Health Canada Apr/21: Canadians and health care professionals that it is conducting a safety review of Xeljanz and Xeljanz XR (tofacitinib) after a clinical trial identified an increased risk of serious heart-related issues and cancer in trial participants.
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Online Extras:

- In observational study of Koreans with atrial fibrillation, warfarin has higher dementia risk compared to NOACS (dabigatran, rivaroxaban, and apixaban), HR=0.87, 95% CI 0.69-0.90
- Scores suggesting risk for unsafe driving:
  - MMSE ≤ 25
  - MoCA ≤ 18
  - Trail Making Tests
    - Part A: Unsafe: ≥ 2 mins or ≥ 2 errors
    - Part B: Unsafe ≥ 3 mins or ≥ 3 errors; Unsure: 2-3 minutes or 2 erros

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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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Farina N, Isaac MGEKN, Clark AR, Rusted J, Tabet N. **Vitamin E** for Alzheimer's dementia and mild cognitive impairment.Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD002854. DOI: 10.1002/14651858.CD002854.pub3. No convincing evidence that vitamin E is of benefit in the treatment of AD or MCI. Future trials assessing vitamin E treatment in AD should not be restricted to alpha-tocopherol.

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We found no evidence that the alpha-tocopherol form of vitamin E given to people with MCI prevents progression to dementia, or that it improves cognitive function in people with MCI or dementia due to AD. However, there is moderate quality evidence from a single study that it may slow functional decline in AD. Vitamin E was not associated with an increased risk of serious adverse events or mortality in the trials in this review. These conclusions have changed since the previous update, however they are still based on small numbers of trials and participants and further research is quite likely to affect the results.

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Drugs with Anticholinergic Effects [5,6,7,8]

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.[9]

Total Anticholinergic Load: both highly anticholinergic drugs plus others (e.g. 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 can cause dry mouth (e.g. 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 mouth 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 lubricants (**MOUTH KOTE**, **BIOTENE GEL**, **ORAL BALANCE GEL**, **MOI-STIR SPRAY** ▼ for Palliative care)
- 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).

Amantadine	154
Amitriptyline	154
ANAFRANIL	154
Anticholinergic	**154**
ARTANE	154
ATARAX	154
Atropine	154
AVENTYL	154
Baclofen	154
Belladonna	154
BENADRYL	154
BENTYLOL	154
Benztropine	154
BONAMINE	154
Brompheniramine	154
BUSCOPAN	154
Carbamazepine	154
Chlordiazepoxide/Clidinium	154
Chlorpheniramine	154
Chlorpromazine	154
CHLOR-TRIPLON	154
Clomipramine	154
Clozapine	154
CLOZARIL	154
COGENTIN	154
COTRIDIN	154
Cyclobenzaprine	154
Cyproheptadine	154
Darifenacin	154
DEMEROL	154
Desipramine	154
DETROL	154
Dicyclomine	154
Dimenhydrinate	154
Diphenoxylate/Atropine	154
Disopyramide	154
DITROPAN	154
Doxylamine	154
ELAVIL	154
ENABLEX	154
Ethopropazine	154
Fesoterodine	154
Flavoxate	154
FLEXERIL	154
Fluphenazine	154
FORMULEX	154
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Sleep/Insomnia	↓ in the efficiency of sleep (amount of time spent in bed sleeping) [24] • 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). This leads to daytime napping & earlier bedtime • Assess possible causative factors (e.g. obstructive sleep apnea nocturia, 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 • Remember: any form of caffeine (even small amounts) can be stimulating e.g. 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 develops[2] ◆Avoid dimenhydrinate: anticholinergic[2] ◆Avoid TCAs: highly anticholinergic, orthostatic hypotension[2] ◆Avoid barbiturates: physical dependence; tolerance to sleep benefits; ↑ risk of overdose at low doses[2] ◆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 care[2] ◆Avoid chloral hydrate: tolerance occurs within 10 days; risk of overdose[2] ◆Avoid chronic use (>90days) of nonbenzodiazepines: similar AE to benzos; minimal improvement in sleep latency & duration[2] ◆Avoid oral decongestants e.g. pseudoephedrine: CNS stimulant effects[2] **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 patient 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 edema (e.g. CCBs nifedipine felodipine, amlodipine, pregabalin, gabapentin) to assess if indicated. Remember for many older adults, a SBP of 150mmHg or even 160mmHg may be suitable, especially if further treatment results in ↑ risk of falls, dizziness, orthostatic hypotension, 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 (e.g. activities of daily living) • Psychological functioning (e.g. cognition, depression) • Social functioning (e.g. social activities, support systems) • Overall health (e.g. 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 **CANVAS**=Canagliflozin Cardiovascular Assessment Study **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 **hr**=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 anti-inflammatory 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 **SGLT2i**=sodium-glucose co-transporter-2 inhibitors **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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Multiple Sclerosis:

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Online Extras

Major and Minor Switching Criteria for Multiple Sclerosis CMSWG 2020			
Consider a therapy change if 1 major criterion is met, or a minor criterion is met with additional worrying sign (e.g. two new lesions or a lesion of significant size)		**Major**	**Minor**
Frequency of Relapses		≥2 relapses in first year of therapy	1 relapse in first 2 years of therapy
Severity of Relapses	Overall severity	Moderate or Severe	Mild
	Functional impairment during relapse?	Yes	No
	Motor, cerebellar, brain stem, or sphincter involvement with relapse?	Yes	No
Recovery	Time to recovery	Incomplete	Within 6 months
	Impairment after recovery?	Yes	No
	EDSS changes at 6 months	> 1 point, or any change if EDSS >5.5	≤1 point, or >1.5 points if baseline is 0
MRI		≥3 new lesions, or >1 spinal cord lesion	1 new lesion

See **Sask. Formulary** for most recent & specific criteria for all MS drugs
SK MS drug program coordinator & nurse educator: 1-866-655-7966 & 306-655-8673
Application forms: http://formulary.drugplan.health.gov.sk.ca/appforms
Special Support calculator: https://www.saskatchewan.ca/residents/health/prescription-drug-plans-and-health-coverage/extended-benefits-and-drug-plan/special-support-program

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EMA Jan/12 European and U.S. regulators are reviewing Novartis AG's (NOVN) **Gilenya** pill for multiple sclerosis after reports of **11 deaths** among patients who took the drug.
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FDA Dec/11 has received a report of a patient with multiple sclerosis (MS) who **died** within 24 hours of taking the first dose of **Gilenya (fingolimod).** At this time, FDA cannot conclude whether the drug resulted in the patient's death.
FDA May/12 warned clinicians on Thursday that "**liberation therapy**," an experimental procedure that uses angioplasty balloons or stents to open narrowed veins in the chest and neck, has not been approved to treat chronic cerebrospinal venous insufficiency (**CCSVI**) and could be dangerous. Liberation therapy has been associated with one death due to a brain hemorrhage and one stroke, says the FDA. Other possible risks include blood clots, cranial nerve damage, and migrating stents.
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.
FDA Aug/15 is warning that a case of definite **progressive multifocal leukoencephalopathy (PML)** and a case of probable PML have been reported in patients taking **Gilenya (fingolimod)** for multiple sclerosis (MS).
FDA Nov/18: Gilenya (**fingolimod**): Drug Safety Communication - Severe Worsening of Multiple Sclerosis After Stopping the Medicine.
FDA Nov/18: Lemtrada (**alemtuzumab**): Drug Safety Communication -Warning That Rare but Serious Cases of **Stroke and Tears in the Lining of Arteries** in the Head and Neck Have Occurred in Patients with Multiple Sclerosis.
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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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MHRA Apr/16 **Natalizumab (Tysabri▼): progressive multifocal leukoencephalopathy**—updated advice to support early detection. Perform a quantitative serum anti-JCV antibody test—including index value—to support risk stratification for progressive multifocal leukoencephalopathy.
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MHRA Apr/16 **Dimethyl fumarate (Tecfidera):** updated advice on risk of progressive multifocal leukoencephalopathy. Cases of progressive multifocal leukoencephalopathy have been reported in patients taking dimethyl fumarate for multiple sclerosis, who all had prolonged lymphopenia.
https://www.gov.uk/drug-safety-update/dimethyl-fumarate-tecfidera-updated-advice-on-risk-of-progressive-multifocal-leukoencephalopathy
MHRA Apr/16 **Fingolimod** (Gilenya▼): risks of **progressive multifocal leukoencephalopathy**, basal-cell carcinoma, and opportunistic infections. The immunomodulatory effects of fingolimod increase the risk of progressive multifocal leukoencephalopathy and opportunistic infections.
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MHRA Dec/17: **Cladribine** (Litak, Leustat) for leukaemia: reports of progressive multifocal encephalopathy (PML); stop treatment if PML suspected
MHRA Dec/17: **Fingolimod** can cause persistent bradycardia, which can increase the risk of serious cardiac arrhythmias.
MHRA Dec/17: **Fingolimod** monitor patients closely for skin cancers.
MHRA Jan/18: **Daclizumab** (Zinbryta▼) & risk of severe liver injury: new restrictions to use and strengthened liver monitoring. The use of daclizumab (daclizumab beta) is now restricted to adults with relapsing multiple sclerosis who have had an inadequate response to at least 2 other disease-modifying therapies (DMTs) and for whom other DMTs are contraindicated or unsuitable.
MHRA Mar/18: **Daclizumab** (Zinbryta▼): suspension and recall for safety reasons; review patients as soon as possible and start alternative therapy.The European Medicines Agency (EMA) has recommended the immediate suspension of the marketing authorisation and recall of daclizumab (Zinbryta) in the EU following reports of serious inflammatory brain disorders, including **encephalitis** and meningoencephalitis, in patients with multiple sclerosis
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MIGRAINE

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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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337. Linde K, Allais G, Brinkhaus B, et al. **Acupuncture for the prevention of episodic migraine**. Cochrane Database Syst Rev. 2016 Jun 28;6:CD001218. The available evidence suggests that adding acupuncture to symptomatic treatment of attacks reduces the frequency of headaches. Contrary to the previous findings, the updated evidence also suggests that there is an effect over sham, but this effect is small. The available trials also suggest that acupuncture may be at least similarly effective as treatment with prophylactic drugs. Acupuncture can be considered a treatment option for patients willing to undergo this treatment. As for other migraine treatments, long-term studies, more than one year in duration, are lacking.
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Migraine: Overview

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Migraine Online Extras

Table 1. Red Flags for Evaluating Acute Headache.

Danger sign or symptoms	Possible diagnoses	Consider the following tests:
First or worst headache of the patient's life	CNS infection, intracranial hemorrhage	Neuroimaging
Focal neurological signs (not typical aura)	Arteriovenous malformation, collagen vascular disease, intracranial mass lesion	Blood tests, neuroimaging
HA triggered by cough, exertion, or sexual intercourse	Mass lesion, subarachnoid hemorrhage	Lumbar puncture, neuroimaging
HA with change in personality, mental status, level of consciousness	CNS infection, intracerebral bleed, mass lesion	Blood tests, lumbar puncture, neuroimaging
Neck stiffness or meningismus	Meningitis	Lumbar puncture
New onset of severe headache in pregnancy or postpartum	Cortical vein/cranial sinus thrombosis, carotid artery dissection, pituitary apoplexy	Neuroimaging
Age > 50 years	Mass lesion, temporal arteritis	Erythorcyte sedimentation rate, neuroimaging
Papilledema	Encephalitis, mass lesion, meningitis, pseudotumor	Lumbar puncture, neuroimaging
Rapid onset with strenuous exercise	Carotid artery dissection, intracranial bleed	Neuroimaging
Sudden onset (maximal intensity occurs within seconds to minutes, **thunderclap headache**)	Bleeding into a mass or arteriovenous malformation, mass lesion (especially posterior fossa), subarachnoid hemorrhage	Lumbar puncture, neuroimaging
Systemic illness with headache (fever, rash)	Arteritis, collagen vascular disease, encephalitis, meningitis	Blood tests, lumbar puncture, neuroimaging, skin biopsy
Worsening pattern	History of medication overuse, mass lesion, subdural hematoma	Neuroimaging
New headache type in a patient with: Cancer, HIV, Lyme disease	**Cancer**: metastasis, tumor; **HIV**: opportunistic infection, **Lyme**: meningoencephalitis	Lumbar puncture, neuroimaging

Table 2. Types of Headaches.

Primary Headaches	**Migraine Without Aura**	At least 5 episodes fulfilling the following criteria: • Headache episodes lasting 4-72 hours (untreated or unsuccessfully treated) • Headache has at least 2 of the following: unilateral location, pulsating quality, moderate or severe pain intensity, aggravated by (or causes avoidance of) routine physical activity (e.g. walking or climbing stairs) • During the headache, the patient experiences at least 1 of the following: nausea, vomiting, photophobia and/or phonophobia

	Migraine With Typical Aura	At least 2 episodes fulfilling the following criteria:
		• Aura consisting of at least 1 of the following, but no motor weakness:
		  ○ Fully reversible visual symptoms including positive features (e.g. flickering lights, spots, or lines) ± negative features (e.g. loss of vision);
		  ○ Fully reversible sensory symptoms including positive features (e.g. pins & needles) ± negative features (e.g. numbness)
		  ○ Fully reversible dysphasic speech disturbance
		• At least 2 of the following:
		  ○ Homonymous visual symptoms ± unilateral symptoms;
		  ○ At least 1 aura symptom develops gradually over ≥ 5 minutes) ± different aura symptoms occur in succession over ≥ 5 minutes;
		  ○ Each symptom lasts 5-60 minutes
		• A headache that fulfills the criteria for migraine without aura begins during the aura or follows the aura within 60 minutes

	Tension-type (Episodic)	***Infrequent Tension-type HA*** At least 10 episodes occurring fewer then 1 day per month on average (fewer than 12 days per year) and fulfilling the following criteria: • Headache lasts 30 minutes to 7 days • Headache has at least 2 of the following: bilateral location, pressing or tightening (nonpulsating) quality, mild or moderate intensity, not aggravated by routine physical activity such as walking or climbing stairs • Both of the following: no nausea or vomiting (± anorexia), either photo- or phono-phobia ***Frequent Tension-type HA*** • At least 10 episodes occurring on more than 1 but fewer than 15 days per month for at least 3 months and fulfilling all of the criteria for infrequent episodic tension-type headache

	Cluster Headache	At least 5 episodes fulfilling the following criteria:
		  ○ Severe or very severe unilateral orbital, supraorbital, or temporal pain lasting 15-180 minutes if untreated
		  ○ HA with at least 1 of the following ipsilateral autonomic symptoms: conjunctival injection or lacrimation, nasal congestion or rhinorrhea, eyelid edema, forehead and facial sweating, miosis or ptosis, restlessness or agitation
		  ○ Headache episodes occur from 1 every other day to 8 per day
		• Episodic Cluster Headache
		  ○ Fulfills all of the above criteria
		  ○ At least 2 cluster periods lasting 7-365 days and separated by pain-free remissions of more than 1 month
		• Chronic Cluster Headache
		  ○ Fulfills all of the above criteria
		  ○ Episodes recur for more than 1 year without remission periods or with remission periods lasting < 1 month

	Other	(e.g. cold stimulus headache)
Secondary Headaches	• Headache attributed to any of the following: head or neck trauma, cranial or cervical vascular disorder, nonvascular intracranial disorder, substance use or withdrawal, infection, disturbance of homeostasis, psychiatric disorder. • Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures.	

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Non-pharmacological & Treatment Option(s) for Non-Motor Symptoms in PD - Use Non-Motor Symptom-Questionnaire (patient/caregiver to complete prior to appt) July 2021

AUTONOMIC DYSFUNCTION NON-MOTOR SYMPTOMS

Bladder dysfunction See RxFiles Urinary Incontinence Chart, page 77-78	Fluid/caffeine restriction, weight loss, exercise (e.g. kegel). - For urgency/frequency, add or ↑ dopamine therapy (e.g. levodopa) or add anticholinergic (e.g. oxybutynin, tolterodine, solifenacin, darifenacin, trospium). - Desmopressin 10-40ug nasal spray or 100-400ucg orally QHS for OH & nocturia. - Botox injection (serotype A) in detrusor muscle to reduce bladder overactivity. - For urinary retention, bethanechol chloride 25-75mg/d.
Choking & Swallowing Difficulties	Avoid hard, dry food, correct eating habits, proper posture while eating, smaller portions, clear mouth before speaking. Refer to speech/occupational therapist or gastroenterologist (rare gastric feeding tube). Increase dopamine drug dose.
Constipation See RxFiles Management of Constipation Chart, page 61-64	Fibre, fluid, fitness. Reduce or discontinue drugs with anticholinergic activity - Bulking agents psyllium, osmotics PEG 3350 - 17g/d, lactulose 30-60 mL BID, stimulants senokot 2-4 tabs qhs, other prucalopride 2mg/d, linaclotide 145 mcg/d, lubiprostone 24ug od-bid, suppositories &/or enemas. - Pyridostigmine MESTINON 30-60mg TID-QID for constipation & orthostatic hypotension. - Domperidone 10mg TID ac meals; probiotics?
Diplopia, Dry Eyes, Visual Abnormalities	Review and discuss driving abilities, refer to optometrist/ophthalmologist. - Increase dopaminergic medications can improve convergence insufficiency. See RxFiles Dry Eyes Chart, page 35-36
Drooling of saliva Chew gum, eat hard candy.	- Atropine 1% soln – 1-2 drops SL once daily or glycopyrrolate 1-2mg/day (2-3 doses). - Botulinum toxin injections 30-50 units into parotid/submandibular glands. - Dopamine therapy (add or increase dose).
Excessive sweating	- Adjust dopaminergic medications to reduce off periods. - Botox injections to the axilla, palms, and soles (rarely required in PD).
Fecal incontinence	Incontinent products (e.g. adult diapers, pads, guards). - Stop drugs that may contribute to fecal incontinence (e.g. laxatives, stools softeners, metformin) &/or increase dopamine medications.
Nausea/Vomiting	If this is due to new medication, symptoms disappear with time. Other options include: - Domperidone 10mg 30 min before levodopa dose, max 10mg TID. - Change in dopamine therapy (e.g. take with meals (no protein with levodopa)).
Orthostatic Hypotension (OH) See RxFiles Q&A Orthostatic Hypotension	Encourage water/salt intake, avoid big meals, ↑ head of bed, compression stockings, education (stand up slowly/carefully, exercises before standing). R/A antihypertensives. - Domperidone 10mg tid, midodrine 2.5-10mg tid or fludricortisone 0.1-0.3mg/d. - Physostigmine (Mestinon) 30-60mg qid can help OH & constipation. - Desmopressin 10-40ug nasal spray or 100-400ucg orally QHS for OH & nocturia.
Sexual Dysfunction	- See RxFiles Erectile Dysfunction Chart & Sexual Function/Dysfunction Chart, p 75 & 76 - If ED, consider phosphodiesterase inhibitors (e.g. sildenafil, vardenafil, tadalafil). - Apomorphine for ED (causes priapism) & acute intermittent "off" episodes. - Other: Papaverine, alprostadil

SENSORY DISORDERS – no treatments available for olfactory/taste dysfunction

Pain See RxFiles Chronic Non-Cancer Pain Chart, page 127	Behavioural, psychological, physical, music, massage, stretching, warm bath. - ↑ dopaminergic therapy or add botulinum toxin. - Agents to treat OH if the pain is linked to autonomic failure coat hanger pain?. - Add antineuropathic gabapentin, pregabalin, lamotrigine, TCAs or antidepressants SNRI, TCAs.

OTHER NON-MOTOR SYMPTOMS

Dermatitis	See GeriRxFiles Dermatology in Older Adults
Leg swelling	Compression stockings, sit with legs raised. Rule out other causes (e.g. medications, heart/renal failure). ↓ dopaminergic therapy or other drugs that may contribute.
Osteoporosis	See RxFiles Osteoporosis Chart, page 145-146, Vitamin D 1000IU/d
Seizures. See RxFiles Seizure Chart, p 165	Vitamin B6 (pyridoxine) deficiency secondary to levodopa/carbidopa can cause seizures. Treat vitamin B6 deficiency to prevent new-onset seizures.
Weight gain pg 55	Increase physical activity, refer to dietitian. - If due to binge eating or impulse control disorder, reduce dose of dopamine agonist. - Consider other drugs associated with weight gain (e.g. quetiapine, SSRIs).
Weight loss	Nutritional supplements Ensure, Boost, percutaneous endoscopic gastronomy may be required (rarely), refer to dietitian. - Adjust dopaminergic therapy or medications that can contribute to weight loss.

COGNITION & MENTAL HEALTH DISORDERS

Cognitive Dysfunction, Dementia See RxFiles – BPSD Chart, p 151-153	Remain cognitively active, regular physical activity, healthy diet, control vascular risk BP, DM, cholesterol, identify other reversible factors (e.g. infection). - ↓/stop medications that can worsen cognitive impairment bzd, anticholinergics. - Add cholinesterase inhibitor (e.g. donepezil, rivastigmine) ☎ ✆ - Dopamine therapy may improve subtle cognitive deficits seen in early PD.
Apathy – difficult to treat; unlikely to be successful ?Freezing, fatigue	Patient/caregiver education to improve patient/caregiver distress. - If apathy occurs during off periods, ↑ dopamine therapy to ↓ off time. - Methylphenidate may be useful, but limited due to side effects.
Depression or Anxiety	CBT. See RxFiles Antidepressants Chart, page 185 or RxFiles – Anxiety Disorder Medication Chart, page 181. - Dopamine agonist ropinirole, pramipexole have mild antidepressant properties. - Add antidepressants used in PD (e.g. Nortriptyline 25-75mg qhs, citalopram 20mg/d, venlafaxine up to 225mg/d, paroxetine up to 40mg/d) - Benzodiazepines not recommended ↑ risk of falls, ataxia, cognitive dysfunction, nabilone?
Hallucinations or Delusions Hallucinations or delusions should NOT be treated if well tolerated. May take 1-4 weeks to resolve.	Look for triggers. Abrupt onset of hallucinations may be acute illness (e.g. infection, dehydration, toxicity, urinary retention/colonic obstruction). - If hallucinations are not caused by an underlying medical condition & are not tolerated, the following step-wise approach can be useful: a. ↓/discontinue sedatives (e.g. antidepressants, benzodiazepines) b. Taper antiparkinson drugs in roughly the following order: (1) anticholinergics=highest risk of inducing confusion/psychosis; (2) amantadine; (3) dopamine agonists; (4) MAO-B inhibitors selegine, rasagiline; (5) COMT inhibitor entacapone; (6) levodopa=best motor benefit & least amount of hallucinations c. Add cholinesterase inhibitors (e.g. donepezil, rivastigmine) ☎ ✆. d. Add quetiapine 25-150mg qhs or clozapine ☎▼ 6.25-75mg qhs, or pimavanserin not availalbe in Canada - AVOID olanzapine, risperidone or any typical neuroleptics worsen motor symptoms.
Impulse Control Disorders (ICD) or Dopamine Dysregulation Syndrome (DDS)	Patient/caregiver education prior to starting dopamine agonist(s), vigilance & screening at each visit. - Reduce or stop dopamine agonist. - Antidepressants - SSRI or SNRI may or may not help. lack evidence

SLEEP DISORDERS

Refer to sleep clinic for assessment of sleep apnea, RLS, REM Sleep Behaviour Disorder

Excessive Daytime Sleepiness	Stimulating daytime environment, bright light therapy, regular physical activity, caffeine 100-200mg bid. - ↓/stop drugs that cause daytime sedation dopamine agonists, anticholinergics, amantadine - Modafinil ☎▼100-400mg/d, atomoxetine 40-80mg/d, methylphenidate?
Insomnia See RxFiles Sleep/Insomnia Chart, pages 193-194	CBT-insomnia (sleep hygiene, stimulus control, sleep restriction, relaxation, bright light therapy). Caution adding sleep meds - ↑ risk of falls. - Z-drugs (e.g. zopiclone 3.75-7.5mg qhs, zolpidem 2mg SL hs), doxepin 3-10mg qhs, trazodone 12.5-25mg qhs, desipramine 10mg qhs, BZD? - Melatonin 0.3-5mg 30-90 minutes before bedtime, nabilone? - Dopaminergic medications (e.g. levodopa/carbidopa CR qhs, levodopa for early morning awakenings, add long-acting agents to the daily regimen)
Rapid Eye Movement (REM) Sleep Behaviour Disorder	Bed safety measures (e.g. moving sharp objects away from bed, bed rails, pillows/mattresses at the side of bed, sleep apart from spouse, etc.). - Stop antidepressants/TCAs - can trigger or worsen REM sleep behaviour disorder. Bupropion is not associated with REM sleep behaviour disorder. - Clonazepam 0.25-2mg HS; helps up to 90% of cases. - Melatonin 3-12mg HS.
Restless Legs Syndrome (RLS)	- See RxFiles Essential Tremor and Restless Legs Syndrome Chart, page 156. - Iron – check ferritin levels and supplement if necessary - Dopamine therapy (e.g. levodopa, pramipexole, ropinirole) - Gabapentin 100-300mg OD-BID or opioids (e.g. codeine 30-180mg/d)

Diagnosis extras

PD can be diagnosed using the Movement Disorder Society (MDS) Clinical Diagnostic Criteria[CAN 2019, grade: GPP]

- The first essential criterion is parkinsonism = bradykinesia with at least 1 of rest tremor or rigidity.
  - Use MDS-Unified Parkinson Disease Rating Scale (UPDRS) for examination.
- Once parkinsonism has been diagnosed:
  - Diagnosis of **Clinically Established PD** requires:
    1. Absence of absolute exclusion criteria;
    2. At least 2 supportive criteria; and
    3. No red flags
  - Diagnosis of **Clinically Probable PD** requires:
    1. Absence of absolute exclusion criteria and
    2. Presence of red flags counterbalanced by supportive criteria
       - If 1 red flag is present, there must also be at least 1 supportive criterion; if 2 red flags, at least 2 supportive criteria are needed.
       - No more than 2 red flags are allowed for this category
- **Supportive Criteria:**
  - Clear and dramatic beneficial response to dopaminergic therapy (e.g. levodopa 600mg/d). During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response, a dramatic response can be classified as:
  - Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document objective (>30% in UPDRS III with change in treatment) or subjective (clearly-documented hx of marked changes from a reliable patient or caregiver) response.
  - Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
    - Presence of levodopa-induced dyskinesia.
    - Rest tremor of a limb.
    - The presence of either olfactory loss or cardiac sympathetic denervations on MIBG scintigraphy.
- **Absolute exclusion criteria:** The presence of any of these features rules out PD:
  - Unequivocal cerebellar abnormalties, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (e.g. sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
  - Downward vertical supraneuclear gaze palsy, or selective slowing of downward vertical saccades
  - Diagnosis of probable behavioural variant frontotemporal dementia or primary progressive aphasia within first 5 years of disease
  - Parkinsonian features restricted to the lower limbs for more than 3 year
  - Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
  - Absence of observable response to high-dose levodopa despite at least moderate severity of disease
  - Unequivocal cortical sensory loss (e.g. graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia.
  - Normal functional neuroimaging of the presynaptic dopaminergic system.
  - Alternative syndrome or condition known to produce parkinsonism but is not PD
- **RED FLAGS:** {Presence of red flags may suggest atypical disease or secondary parkinsonism}
  - Rapid progression of gait impairment requiring regular use of wheelchair within 5 yr of onset
  - A complete absence of progression of motor symptoms or signs over 5 or more year unless stability is related to treatment
  - Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube or gastrostomy feeding) within first 5 y
  - Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
  - Severe autonomic failure in the first 5 years of disease. This can include:
    - Orthostatic hypotension = orthostatic decrease in BP within 3 min of standing by at least 30 mmHg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
    - Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women) that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction.
  - Recurrent (>1/y) falls because of impaired balance within 3 yr of onset
  - Disproportionate anterocollis (dystonic) or contracutres of hand or feet within the first 10 yrs.
  - Absence of any of the common nonmotor features of disease despite 5 year disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behaviour disorder), autonomic dysfunction (e.g. constipation, daytime urinary urgency, symptomatic orthostatsis), hyposmia, or psychiatric dysfunction (e.g. depression, anxiety, hallucinations)
  - Otherwise unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response).
  - Bilateral symmetric parkinsonism. The patient or caregive reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination.

- Consider ^{123}I-FP-CIT SPECT scanning if uncertainty between PD & nondegenerative parkinsonism or tremor disorders. Routine functional imaging, PET, CT or MRI brain scanning or objective olfactory testing are not routinely recommended in the diagnosis of PD.
- **SUPPORTIVE CRITERIA**: Response to dopaminergic therapy$_{\text{levodopa 600mg/d}}$; levodopa-induced dyskinesia; rest tremor of a limb; olfactory loss or cardiac sympathetic denervations on MIBG scintigraphy.
- **DISEASE PROGRESSION**: may be more rapid if: onset >70yr, rigid, bradykinesia, dementia, or previous levodopa use but NOT as rapid if: male or resting tremor dominant. ↑ Mortality if: mild cognitive impairment, postural imbalance and gait disorder[86]

DRUG-INDUCED PARKINSONISM (DIP)

- **HIGH RISK DRUGS:** Typical neuroleptics[PD symptoms can occur 2 months after starting] (haloperidol, pimozide?, chlorpromazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, flupentixol, zuclopenthixol), atypical neuroleptics (aripiprazole, asenapine, brexpiprazole, loxapine, lurasidone, olanzapine, paliperidone, risperidone), tetrabenazine, methyldopa, metoclopramide, flunarizine[PD symptoms can occur 6 months after starting], valproate.
- **INTERMEDIATE RISK DRUGS:** Calcium channel blockers (amlodipine, diltiazem, verapamil), antiepileptics (phenytoin, levetiracetam), lithium, tamsulosin (observational), venlafaxine, ziprasidone.
- **LOW RISK DRUGS**: Amiodarone, antidepressants (SSRIs-citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline; TCAs-amitriptyline, clomipramine, MAOIs-moclobemide, phenelzine, others-mirtazapine, trazodone), immunosuppressive (cyclosporine, tacrolimus), antibiotics (clotrimoxazole, rifampicin), antivirals (acyclovir, vidarabine, ritonavir, ribavirin), amphotericin B, hormones (levothyroxine, medroxyprogesterone, epinephrine), domperidone, lorazepam, hydroxyzine, lovastatin, quetiapine.
- **CASE REPORTS:** Bupivacaine, bupropion, captopril, carbamazepine, chloroquine, diazepam, interferon apha, lamotrigine, meperidine, paclitaxel, peginterferon, pindolol, pregabalin, procaine, pyridostigmine, vincristine.
- **Toxins** - carbon monoxide, carbondisulfide, cyanide, hydrocarbons, manganese, methanol ± ethylenglycol, organochlorides, organophosphates.
- **Street drugs** – Ecstasy, heroin, methamphetamine, methcathionine, MPTP.

Motor Symptoms	Description
Bradykinesia* ~70% of patients with PD	Slowness & progressively smaller movements (hypokinesia) as an individual repeats a task (e.g. tapping index finger & thumb, opening & closing fist) multiple times in a row. Slowness of all movements/walking.
Rigidity* ~90% of patients with PD	Involuntary, velocity dependent resistance to passive movement of a joint (e.g. elbow, wrist) by an examiner, with or without a cogwheel phenomenon. Lead pipe, cogwheel often in neck, trunk & limbs.
Rest tremor* ~70% of patients with PD	A 4- to 6-Hz tremor in a fully resting limb; temporarily disappears when the limb is held outstretched & then returns (reemergent tremor) & is not present during the movement. Rhythmic, asymmetric, hands (pill rolling), feet, lip or jaw (not usually head or neck).
Postural instability	Balance impairment affecting ability to change or maintain postures (walking or standing); typically a late PD feature. Shuffling gait, narrow base, festination, freezing & falls.
Other: Micrographia (small handwriting), decreased arm swing, short step length, soft voice	

*Indicates a primary feature.

SURGERY

- If poor medical control consider surgery (e.g Deep Brain Stimulation (DBS): subthalamic nucleus (STN), globus pallidus (GPi), thalamus; implant stem cells, focused ultrasound subthalamotomy).
- STN DBS has also been studied in early-stage PD (n=28, follow-up=5 years) resulting in lower levodopa dose and less resting tremor.
- DBS may help tremor, on time, bradykinesia, rigidity, dyskinesia, QoL, ↓ levodopa dose;
  - DBS may not help gait, balance/fall, speech &/or swim, cognitive?/functional performance
- Surgical procedure **AE**: infections (6%), migration or misplacement of the leads (5%), lead fractures (5%), intracranial hemorrhage (3%) and skin erosion (1%).
- Long-term **AE**: eyelid opening apraxia (2-30%), dysarthria or hypophonia (4-17%), speech/gait disturbances (14%), postural instability (13%), weakness, dyskinesia, weight gain (8%), decline in verbal fluency, risk of injury during water-related activities (e.g. swim, bath) because of loss of coordination.

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EXTRA:

=↓ dose-renal dysfx =↓ dose-liver dysfx **ç**=scored tab **χ**=Non-formulary SK ☎=Exception Drug Status SK. ⊗=not covered NIHB =prior NIHB ▼=covered-NIHB Ⓟ=concern if given pre-op ✓=official indication **ac**=before meals **^{123}I-FP-CIT SPECT**=^{123}I-ioflupane single single-photon emission computed tomography **ACh**=anticholinergic **AUC**=area under the curve **BP**=blood pressure **cc**=with meal **BLT**=bright light therapy, **BT**=bladder training **CADTH**=Canadian Agency for Drugs and Technologies in Health **CDEC**=Canadian Drug Expert Committee **CNS**=central nervous system **CR**=control release **CT**=computed tomography **d**=day **DA**=dopamine agonist **D1,2,3,4**= dopamine receptors subtypes **D/C**=discontinue **dx**=disease **EPS**=extrapyramidal symptoms **fx**=function g=generic **g**=gram **GI**=gastrointestinal **GPi**=globus pallidus **HR**=heart rate **HS**=bedtime **IR**=immediate release **l-dopa**=levodopa **MDS**=Movement Disorder Society **MPTP**=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine **MRI**=magnetic resonance imaging **NMS**=neuroleptic malignant syndrome **N/V**=nausea/vomiting **PK**=pharmacokinetic **PET**=positron emission tomography **pt**=patient **ptsd**=post-traumatic stress disorder **RF(s)**=risk factor(s) **SAP**=Special Access Programme **STN**=subthalamic nucleus **sx**=symptoms **tbi**=traumatic brain injury **tx**=treatment **t½**=half-life **UPDRS**=Unified Parkinson's Disease Rating Scale (**0**=no disability;**176**=total disability) **URI**=upper respiratory infection, **Wt**=weight

TREATMENT OPTIONS & GOALS OF THERAPY

- Maintain acceptable levels of function, independence & QoL.
- Minimize acute/long-term AE of drugs for motor & non-motor symptoms of PD.

Definitions:

Impulse control disorders (ICD) are classically identified as problem gambling, shopping, binge eating, craving sweets and hypersexuality; however, any behaviour that is excessive, out of keeping from previous behaviour and impairs occupational or relational functioning may be an impulse control disorder. (e.g. painting, hobbyism or going on long "walk-abouts").

Dopamine Dysregulation Syndrome (DDS) is another form of ICD, similar to an "addiction" to levodopa. Patients with DDS experience severe anxiety and irritation during off periods, and will take excessive medication to prevent any sing of an off period even without their physician's approval.

INVESTIGATIONAL THERAPY:

Nilotinib TASIGNA$^{\chi\otimes}$; protein-tyrosine kinase inhibitor for Philadelphia chromosome positive chronic myeloid leukemia; 150-300mg po daily, $1000-$2000/month, **AE**: falls, musculoskeletal, respiratory, GI, ↑pancreatic enzymes (rare), sudden cardiac death (rare); acceptable safety profile, but worsened MDS-UPDRS-3 ON scores compared to placebo, and no difference in MDS-UPDRS-3 OFF from baseline to 6 months, low CSF exposure and lack of biomarkers.

Ambroxol (not available in North America); commonly used as cough suppressant; 420mg TID in PD (n=18, small study), **AE**: nausea, vomiting, loose stool, acid reflux

Carbidopa higher dose (65mg, 105mg) compared to carbidopa 25mg in combination with levodopa and entacapone has helped improve "off" times (~1.5 hours) and increase in "on" times (~1.4 hours), but not commercially available in Canada. Up to 400mg/d has been tested as tolerable and safe.

IPX066 – combined immediate- and sustained-release carbidopa capsule with 1:4 ratio of carbidopa to levodopa, 145mg, 245mg or 390mg tid comparable to 300mg, 500mg, and 800mg levodopa daily, respectively.

Isradipine 5mg bid x 3 years did not slow down the progression of early-stage Parkinson Disease not treated with dopaminergic antiparkinson drugs, **AE**: dizziness, edema

Foslevodopa/foscarbidopa SC infusion

Varenicline CHAMPIX for gait or balance disorders?

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DOPAMINE AGONISTS

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HEALTH CANADA NOTIFICATIONS

Health Canada Jan/17 is advising Canadians that it has seized three unauthorized workout supplements from Reflex Supplements at #105–10712, 78 Ave., Grande Prairie, AB. "**Animal PM**" is labelled to **contain L-dopa** while "Blade" is labelled to contain yohimbine.

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 Jul/17: Man XXX has undeclared **levodopa** by the Australia Therapeutic Goods Administration.
Health Canada Aug/07: Eli Lilly Canada advises Healthcare Professionals that they will **cease sale of Permax** August 30, 2007 due to risk of cardiac valvulopathy.

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Investigational: bumetanide 0.1-0.3mg/kg bumetanide for neonatal seizures; cannabidiol (CBD) 25-50mg/kg/day for drug-resistant seizures in tuberous sclerosis complex; ketamine infusion+midazolam for super-refractory status epilepticus.

Therapeutic Drug Monitoring: the following ASM can be measured via plasma or serum; however, the relationship between level and clinical efficacy is not well established. May be used to assess compliance.

Drug	Turn around time in SK (approximate))	Therapeutic Range
Lamotrigine	5 days	
Levetiracetam	4 days	70-270 umol/L
Oxcarbazepine metabolite	1-3 days	12-140 umol/L (trough)
Gabapentin	5 days – 3 weeks (Toronto)	
Clonazepam	3 days	60-250 nmol/L
Clobazam	3 days	150-1000 nmol/L
Lacosamide	2 weeks (MAYO clinic)	
Topiramate	5 days – 2 weeks (Toronto)	

Antiseizure Medications: Suggested Place in Therapy SIGN '21

	Lennox-Gastaut syndrome	Infantile spasms, West syndrome	Refractory seizures associated with tuberous sclerosis complex	Infantile spasms with tuberous sclerosis	Dravet syndrome
1st line	Valproate	Adrenocorticotropic hormone (ACTH), tetracosactide, prednisolone, vigabatrin	Everolimus (≥2yr)	Vigabatrin	Valproate
Adjunctive	**Adjunctive** rufinamide (≥4yr), clobazam (≥2yr), lamotrigine (≥2yr), topiramate (≥2yr), cannabidiol with clobazam (≥2yr)				**Adjunctive** stiripentol or clobazam (≥3yr), cannabidiol with clobazam (≥2yr)

ASM affecting hormonal (e.g. estrogen) failure[1069]
Likely to cause hormonal failure: carbamazepine, eslicarbazepine, oxcarbazepine, perampanel ≥ 12 mg/d, phenobarbital, phenytoin, primidone, rufinamide, topiramate
Less likely to cause hormonal failure: brivaracetam, clobazam, ethosuximide, gabapentin, lacosamide, levetiracetam, lamotrigine, pregabalin, vigabatrin, stiripentol

Free online seizure e-diary: seizuretracker.com

Clinical Decision Rule for Predicting Recurrent Febrile Seizures[1078]

Risk Factor	Points	Total Points	Risk of recurrent febrile seizure (likelihood, %)
Age < 18 months	1	0	13%
Body temperature < 40˚C at the time of the seizure	1	1	23%
Duration of fever < 1 hour	1	2	32%
Family hx of febrile seizure	1	3	62%
Total		4	76%

Abbreviations:

- ☎=exception drug SK ✗ =Non formulary SK ✆=prior approval NIHB ⊗=not covered NIHB ▼=covered NIHB =↓dose for renal dysfx ς =scored tab þ=porphyria concern ✓=Useful for/in **ADJ**=adjunctive **ADV**=advantage **AE**=adverse effect **Alt**=alternate **ASM**=antiseizure medications **AV**=atrioventricular **BZ**=benzodiazepine **CBC**=complete blood count **CBZ**=carbamazepine **cc**=with food **CHC**=combined hormonal contraceptive (e.g., OC, patch, ring)

CI=contraindication **CNS**=central nervous system **CR**=control release **DOAC**=direct oral anticoagulant **DRESS**=drug reaction with eosinophilia and systemic symptoms **dx**=disease **esp**=especially **EEG**=electroencephalography **EC**=enteric coated **Eq**=equation **fx**=function **GI**=gastrointestinal **GTC**=generalized tonic clonic **hb**=hemoglobin **hx**=history **LD**=loading dose **LFT**=liver function test **LGS**=Lennox-Gastaut syndrome **MAOI**=monoamine oxide inhibitor **MRI**=magnetic resonance imaging **N/A**=not applicable **N/V**=nausea/vomiting **OC**=oral contraceptive **Peds**=pediatric dose **POP**=progestin only pill **PRN**=as needed **TCA**=tricyclic antidepressant **SAP**=Special Access Progam **SCr**=serum creatinine **SLE**=systemic lupus erythrematosus **SJS**=Stevens-Johnson syndrome **sz**=seizure **TENS**=toxic epidermal necrolysis syndrome **TFT**=thyroid function test **URTI**=upper respiratory tract infection **yrs**=years

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per 1,000, as compared to 0.37 per 1000 in the reference population for that registry. The prevalence of oral clefts noted in the NAAED registry is also higher than the background prevalence of non-syndromic oral clefts reported in the literature, including studies from the United States, Australia and Europe. While different studies have differing results due to geographic and case ascertainment variations, the reported range is 0.50 to 2.16/1000 3-17. To assist with the assessment of risk, analysis of data from additional pregnancy registries, with approximately 2200 additional lamotrigine monotherapy first trimester exposures has been conducted, and 4 additional non-syndromic cases of oral cleft have been identified. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/lamictal_2_hpc-cps_e.html (see also Pharmacist's Letter Sept 2006.)
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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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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
- External condoms [aka 'male condoms'] – 11 to 16 may get pregnant
- Diaphragm – 15 may get pregnant
- Sponge – 16 to 32 may get pregnant
- Internal condoms [aka 'female condoms'] – 20 may get pregnant
- Spermicide alone – 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 Oct/11 released the final report of an FDA-funded study looking into the risk for venous thromboembolism (VTE) in women taking oral contraceptives containing drospirenone. As previously reported by Medscape Medical News, on September 26 the FDA said preliminary findings from the study indicate that women who use **drospirenone-containing birth control pills have an approximately 1.5-fold increase** in the risk of developing blood clots relative to women using other types of hormonal contraceptives.
FDA Drug Safety Communication Sept/11: Safety review update on the possible increased risk of blood clots with birth control pills containing drospirenone. http://www.fda.gov/Drugs/DrugSafety/ucm273021.htm (Accessed November 29th, 2011).
FDA Apr/12 has completed its review of recent observational (epidemiologic) studies regarding the risk of blood clots in women taking drospirenone-containing birth control pills.Based on this review, FDA has concluded that **drospirenone**-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills. . Report that some epidemiologic studies reported as high as a three-fold increase in the risk of blood clots for drospirenone-containing products when compared to products containing levonorgestrel or some other progestins, whereas other epidemiological studies found no additional risk of blood clots with drospirenone-containing products.
FDA Nov/16 **Essure** labeling now includes the addition of a boxed warning and a Patient Decision Checklist, both intended to support patient counseling and understanding of benefits and risks associated with Essure, as well as what to expect during and after the Essure procedure. The boxed warning includes safety statements to clearly communicate significant side effects or adverse outcomes associated with this device and information about the potential need for removal.
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Health Canda June/10 **MIRENA** (Levonorgestrel-Releasing Intrauterine System) - Potential Risk of Uterine Perforation - Bayer Inc. Bayer Inc., in collaboration with Health Canada, would like to remind you of important safety information regarding reports of uterine perforation in women treated with MIRENA.
Health Canada Dec/11 has completed a safety review of drospirenone-containing oral contraceptives (marketed under the brand names Yasmin and Yaz) with respect to the risk of blood clots (venous thromboembolism, or VTE). The review determined that **drospirenone-containing birth** control pills may be associated with a risk of blood clots that is **1.5 to 3 times higher than other birth control pills**.
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.
Health Canada Nov/17 **MIFEGYMISO (mifepristone and misoprostol tablets) - Updates** to Product Monograph and Risk Management Plan. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/65030a-eng.php
Health Canada Dec/17 is advising consumers and health care professionals that complaints have been received for packages of **Alesse 21 (21 active pills) and Alesse 28** (21 active pills, 7 that contain no hormones). The blister packages for both contained an active (pink) pill that was roughly half the proper size.
Health Canada Dec/17 and Pfizer Canada Inc. have received reports for packages of **ALESSE 21 and ALESSE 28** where the blister packages contained a single active (pink) tablet that was **broken**. This could reduce the dose of hormones and potentially result in an unintended pregnancy due to insufficient action of the contraceptive hormones levonorgestrel and ethinyl estradiol.
Health Canada Feb/18: **Alysena 28** birth control pill: One lot recalled due to chipped pills, which may reduce effectiveness in preventing pregnancy. Health Canada is informing Canadians that all lots of both Alysena 21 and Alysena 28 may have **chipped pills**.
Health Canada Jun/18: Pfizer Canada Inc. has notified Health Canada that it has received complaints of **broken or chipped pills involving Demulen 30**, a prescription birth control pill.
Health Canada Apr/19 is informing Canadians that the prescribing and patient information for **Mifegymiso** has been updated to reflect that an ultrasound is no longer required before the drug is prescribed.
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Lopez LM, Grimes DA, Chen-Mok M, et al. Hormonal contraceptives for **contraception in overweight or obese women**. Cochrane Database Syst Rev. 2010 Jul 7;7:CD008452. Body weight addresses overall body size, while BMI generally reflects the amount of fat. Only one of three studies using BMI found a higher pregnancy risk for overweight women. The efficacy of implants and injectable contraceptives may be unaffected by body mass. The field could use trials of contraceptive methods with groups stratified by BMI. The current evidence on effectiveness by BMI is limited. However, the contraceptive methods examined here are still among the most effective when the recommended regimen is followed.

Lopez LM, Edelman A, Chen-Mok M, Trussell J, Helmerhorst FM. **Progestin-only contraceptives: effects on weight**. Cochrane Database Syst Rev. 2011 Apr 13;4:CD008815. We found little evidence of weight gain when using POCs. Mean gain was less than 2 kg for most studies up to 12 months, and usually similar for the comparison group using another contraceptive.

Lopez LM, Hiller JE, Grimes DA, et al. **Education** for contraceptive use by women after childbirth. Cochrane Database Syst Rev. 2012 Aug 15;8:CD001863. The overall quality of evidence was moderate. Half of these postpartum interventions led to fewer repeat pregnancies or births or more contraceptive use.

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Lopez LM, Edelman A, Chen-Mok M, et al. **Progestin-only contraceptives: effects on weight**. Cochrane Database Syst Rev. 2011 Apr 13;4:CD008815. We found little evidence of weight gain when using POCs. Mean gain was less than 2 kg for most studies up to 12 months, and usually similar for the comparison group using another contraceptive. Appropriate counseling about typical weight gain may help reduce discontinuation of contraceptives due to perceptions of weight gain.

Lopez LM, Newmann SJ, Grimes DA, et al. **Immediate start of hormonal contraceptives** for contraception. Cochrane Database Syst Rev. 2012 Dec 12;12:CD006260. doi: 10.1002/14651858.CD006260.pub3. We found limited evidence that immediate start of hormonal contraception reduces unintended pregnancies or increases method continuation. However, the pregnancy rate was lower with immediate start of DMPA versus another method.

Lopez LM, Stockton LL, ChenM, SteinerMJ, GalloMF. **Behavioral interventions for improving dual-method contraceptive use**. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD010915. DOI: 10.1002/14651858.CD010915.pub2. We found few behavioral interventions for improving dual-method contraceptive use and little evidence of effectiveness. Amultifaceted program showed some effect but only had self-reported outcomes. Two trials were more applicable to clinical settings and had objective outcomesmeasures, but neither showed any effect.The included studies had adequate information on intervention fidelity and sufficient follow-up periods for change to occur.

Lopez LM, Grimes DA, Schulz KF, et al. Steroidal contraceptives: effect on **bone fractures** in women. Cochrane Database Syst Rev. 2014 Jun 24;6:CD006033. Whether steroidal contraceptives influence fracture risk cannot be determined from existing information. The evidence quality was considered moderate overall, largely due to the trials of DMPA, implants, and the patch versus ring. The COC evidence varied in quality but was low overall. Many trials had small numbers of participants and some had large losses. Health care providers and women should consider the costs and benefits of these effective contraceptives. For example, injectable contraceptives and implants provide effective, long-term birth control yet do not involve a daily regimen. Progestin-only contraceptives are considered appropriate for women who should avoid estrogen due to medical conditions.

Lopez LM, Grey TW, Stuebe AM, et al. **Combined hormonal versus nonhormonal versus progestin-only contraception in lactation**. Cochrane Database Syst Rev. 2015;(3):CD003988. Results were not consistent across the 11 trials. The evidence was limited for any particular hormonal method. The quality of evidence was moderate overall and low for three of four placebo-controlled trials of COCs or POPs. The sensitivity analysis included six trials with moderate quality evidence and sufficient outcome data. Five trials indicated no significant difference between groups in breastfeeding duration (etonogestrel implant insertion times, COC versus POP, and LNG-IUS). For breast milk volume or composition, a COC study showed a negative effect, while an implant trial showed no significant difference. Of four trials that assessed infant growth, three indicated no significant difference between groups. One showed greater weight gain in the etonogestrel implant group versus no method but less versus DMPA.

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Birth Control

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Birth Control Online Extras:

Table 3: 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)

Link to CDC – Medical Eligibility for Contraceptive Use – detailed chart:
https://www.cdc.gov/reproductivehealth/contraception/pdf/summary-chart-us-medical-eligibility-criteria_508tagged.pdf

BCP	**171**
Birth Control	171
CHC	**171**
COC	**171**
Copper IUD	171
DEPO-PROVERA	171
Estradiol	171
Etonogestrel	171
EVRA	171
FLEXI-T	171
IMPLANON	171
KYLEENA	171
Levonorgestrel	171
LIBERTE	171
Medroxyprogesterone	171

MICRONOR	171
Mini-Pill	171
MIRENA	171
MONA-LISA	171
NEXPLANON	171
Norelgestromin	171
NORPLANT	171
NUVARING	171
Oral Contraceptive	**171**
POP	171
Progestin Injection	171
Sponge	172
ANNOVERA	172
BCP	**172**
CHC	**172**
COC	**172**
Condom	172
DEPO-PROVERA	172
Diaphragm	172
Estradiol	172
Etonogestrel	172
EVRA	172
FLEXI-T	172
IMPLANON	172
JENCYCLA	172
KYLEENA	172
Levonorgestrel	172
LIBERTE	172
LILETTA	172
MICRONOR	172
MIRENA	172
MONA-LISA	172
MOVISSE	172
NEXPLANON	172
Norelgestromin	172
NUVARING	172
Oral Contraceptive	**172**
PREMARIN	172
Segesterone	172
SLYND	172
Spermicide	172
SKYLA	172

TWIRLA	172
XULANE	172
ZAFEMY	172
Birth Control	172
Copper IUD	172
Estrogen	171
OCP	171
Progestin	171

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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.
FDA Nov/16 **Essure** labeling now includes the addition of a boxed warning and a Patient Decision Checklist, both intended to support patient counseling and understanding of benefits and risks associated with Essure, as well as what to expect during and after the Essure procedure. The boxed warning includes safety statements to clearly communicate significant side effects or adverse outcomes associated with this device and information about the potential need for removal.
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Health Canda June/10 **MIRENA** (Levonorgestrel-Releasing Intrauterine System) - Potential Risk of Uterine Perforation - Bayer Inc. Bayer Inc., in collaboration with Health Canada, would like to remind you of important safety information regarding reports of uterine perforation in women treated with MIRENA.

Health Canada Dec/11 has completed a safety review of drospirenone-containing oral contraceptives (marketed under the brand names Yasmin and Yaz) with respect to the risk of blood clots (venous thromboembolism, or VTE). The review determined that **drospirenone-containing birth** control pills may be associated with a risk of blood clots that is **1.5 to 3 times higher than other birth control pills**.

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.

Health Canada Nov/17 **MIFEGYMISO (mifepristone and misoprostol tablets) - Updates** to Product Monograph and Risk Management Plan. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/65030a-eng.php

Health Canada Dec/17 is advising consumers and health care professionals that complaints have been received for packages of **Alesse 21 (21 active pills) and Alesse 28** (21 active pills, 7 that contain no hormones). The blister packages for both contained an active (pink) pill that was roughly half the proper size.

Health Canada Dec/17 and Pfizer Canada Inc. have received reports for packages of **ALESSE 21 and ALESSE 28** where the blister packages contained a single active (pink) tablet that was **broken**. This could reduce the dose of hormones and potentially result in an unintended pregnancy due to insufficient action of the contraceptive hormones levonorgestrel and ethinyl estradiol.

Health Canada Feb/18: **Alysena 28** birth control pill: One lot recalled due to chipped pills, which may reduce effectiveness in preventing pregnancy. Health Canada is informing Canadians that all lots of both Alysena 21 and Alysena 28 may have **chipped pills**.

Health Canada Jun/18: Pfizer Canada Inc. has notified Health Canada that it has received complaints of **broken or chipped pills involving Demulen 30**, a prescription birth control pill.

Health Canada Apr/19 is informing Canadians that the prescribing and patient information for Mifegymiso has been updated to reflect that an ultrasound is no longer required before the drug is prescribed.

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were similar for the methods compared. The patch group had better compliance than the COC group. Compared to COC users, patch users had more side effects. Ring users generally had fewer adverse events than COC users but more vaginal irritation and discharge. The patch could lead to more discontinuation while the vaginal ring showed little difference. High losses to follow up can affect the validity of the results.

Lopez LM, Grimes DA, Gallo MF, Schulz KF. Skin patch and **vaginal ring versus combined oral contraceptives** for contraception. Cochrane Database Syst Rev. 2010 Mar 17;3:CD003552. Effectiveness was similar for the methods compared. The patch could lead to more discontinuation while the vaginal ring showed little difference. The patch group had better compliance than the COC group but more side effects. Ring users generally had fewer adverse events than COC users but more vaginal irritation and discharge.

Lopez LM, Newmann SJ, Grimes DA, Nanda K, Schulz KF. Immediate start of hormonal contraceptives for contraception. *Cochrane Database Syst Rev.* 2008;(2):CD006260.

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RxFiles Peri-Pregnancy Extras: Pregnancy & Lactation Lifestyle Information

Prepared by Lynette Kosar BSP,MSc www.RxFiles.ca Nov 2020

	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 aerobics(low impact), strength training, stationary cycling, swimming 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, HA, dizzy or faint. ⇨Targeted HR during pregnancy: age (beats/min) <20 (140-155), 20-29 (135-150), 30-39 (130-145), ≥40 (125-140) If **obese** (BMI ≥30kg/m²): age 20-29 (102-124), 30-39 (101-120) ⇨ "Talk test" can also be used to monitor intensity ACOG'15 • 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 see chart pg 204	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,MTX, sulfonamide, trimethoprim, metformin, 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/m², epilepsy, hemolytic anemia, smoker **Is too much folic acid harmful?** Likely not (water-soluble vitamin). May mask vitamin B₁₂ deficiency; consider maternal multivitamin with vitamin B₁₂ 2.6mcg/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⁻ 220mcg, $8 - **PregVit/PregVit folic 5**[Rx✗⊗] Fe⁺⁺ 35mg, folic acid 1.1/5mg, Ca⁺⁺ 300mg, Vit D 250IU, I⁻150mcg. 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:** 250mcg/d total (max 500mcg/d) & maternal multivit with ≥150mcg. 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 **Fish & Mercury Levels during Pregnancy & Breastfeeding**: Health Canada recommends 2 servings of fish/wk (75g=2.5oz=½ cup); FDA'17 2-3 servings/wk. Limit fish with ↑ mercury levels (fresh/frozen tuna, shark, swordfish, marlin, orange roughy, king mackerel, escolar) to 150g/mon. Limit canned albacore (white) tuna to 300g/wk.[34] Refer to Health Canada's Food Safety for Pregnant ♀ for info on other foods to avoid (certain cheeses, deli meats) http://www.hc-sc.gc.ca/hl-vs/alt_formats/pdf/iyh-vsv/food-aliment/pregnant-enceintes-mar-2010-eng.pdf	⇨ 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.
Body Weight [35]	⇨Encourage BMI <30kg/m² (ideal 18.5-24.9kg/m²). Promote diet & exercise to ↓ weight. If obese, start folic acid see above. ⇨Screen: diabetes (i.e. FBG, A1C) ⇨Pregnancy complications with BMI >30kg/m²: (also risk BMI<18.5) • ↑ 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)	Pre-pregnancy BMI[36] / **Rate** of weight gain (mean) 2nd & 3rd trimester kg (lb)/week / **Total** weight gain kg (lb) (based on ≤2kg (4.4lb) weight gain in 1st trimester) <18.5 / 0.5 (1) / 12.5-18 (28-40) 18.5-24.9 / 0.4 (1) / 11.5-16 (25-35) 25-29.9 / 0.3 (0.6) / 7-11.5 (15-25) ≥30 / 0.2 (0.5) / 5-9 (11-20) ⇨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.lllc.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 201 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 or varenicline

RxFiles Peri-Pregnancy Extras continued…

Contraception [40] see charts pg 169-170 and pg 171-172

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.

⇨ ! 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 ↓ placental abruption (**NNT=333**) & ↑ risk of P GestHTN and premature rupture of membranes (**NNH=19**).

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Postpartum Depression:

- Edinburgh Postnatal Depression Scale: http://www2.aap.org/sections/scan/practicingsafety/Toolkit_Resources/Module2/EPDS.pdf
- more evidence in postpartum population compared to PHQ-9
- was developed for use at the 6-8 week postnatal visit; 10 questions; self-administered based on how the mother has felt during the *previous week*.
- Interpretation of Scale: ≥10 (range 9-13) possible depression; maximum score 30

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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Health Canada June 2021 has completed a safety review confirming that the use of non-steroid anti-inflammatory drugs (NSAIDs)—such as acetylsalicylic acid (aspirin), ibuprofen, naproxen, diclofenac and celecoxib —starting from approximately 20 weeks of pregnancy or later, may cause rare but serious kidney problems in an unborn baby. This can lead to low levels of amniotic fluid and possible complications, such as impaired lung maturation and loss of joint **movement (limb contractures) in the newborn baby.**
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Extra:

Ulipristal FIBRISTAL ☎▼ x3mons 5mg tab **D/C by company Sept 2020: liver AEs** [38]	Selective progesterone receptor modulator; inhibits cell growth & promotes apoptosis			**ADV:** controls bleeding related to uterine leiomyomas & fast onset of amenorrhea (7-10 days)
	5mg po daily. Start during the first 7 days of menstrual cycle. Safety not established in renal impairment: Monitor closely if used	$1100 for 3 months	**AE**: hot flashes, HA, dyslipidemia, breast pain, ↑ **LFTs** **CI**: pregnant, BF & with breast, uterine, ovarian or cervical CA. Known liver dx **DI** [3A4]: CBZ, efavirenz, perampanel, SJW; may ↑P-gp substrates [eg dabigatran etexilate, dig] OCs & progestin-only pills should not be given in combination with Ulipristal	• Menstrual blood loss: 91% controlled vs 19% in placebo (noninferior & more sustained effect than leuprolide acetate; effect may persist up to 6 months) • Other: ↓leiomyoma [volume] (≤31% vs placebo ↑3%); indicated: 1-2 courses x **≤3 months** • EMA[2018]: Risk of rare, but serious liver injury [AST/ALT **M**: pre tx & monthly. Repeat 2-4 weeks post treatment]
Severe liver injury [1.5:100,000 pts], fatal liver injury [0.1:100,000 pts]				

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EXTRAS – RxFiles – Abnormal Uterine Bleeding – Tx Chart

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 (leiomyomas) & 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
4. Elagolix ORILISSA: GnRH antagonist; ↓ menstrual blood loss (reduction in baseline bleeding by ≥50% = 31% vs. 94%); ↓ uterine fibroid volume (mean percentage change since baseline 4.6% vs. -39.6%). Potential for add-back therapy to ↓ adverse events[36]

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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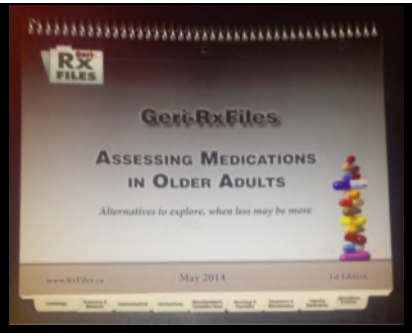

Abnormal Uterine Bleeding Comparison Chart

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Online Extras

Trials: **WHI** (CHD, breast ca,…), **WHIMS** (memory/dementia age ≥65; **WHIMSY** age 50-55), **WHISCA** (cognitive fx); **EMS** (E2 on memory); **HERS** (CEE+MPA in 2° CHD prevention); **ESPRIT** (E2 in 2° MI prevention); **ULTRA** (low-dose transdermal E2 0.014mg/d on non-CV outcome); **WISDOM** (long-duration CEE+MPA).

Discontinued products: conjugated estrogen **C.E.S.** tabs, estrone **OGEN** tabs, conjugated estrogen + medroxyprogesterone **PREMPLUS** tabs, estradiol + norethindrone **FemHRT** tabs, estradiol **ESTRADERM** patch, estradiol **VIVELLE** patch, estradiol + norethindrone **ESTRACOMB** patch, estradiol alone followed by estradiol + norethindrone **ESTALIS-SEQUI** patches, estradiol gel + progesterone tabs **ESTROGEL PROPAK**, testosterone + estradiol **CLIMACTERON** inj.

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 warrants 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

Testosterone Therapy

Testosterone therapy may be used for postmenopausal women to treat hypoactive sexual desire disorder. Low dose testosterone had moderate effect, 1 additional satisfying sexual event per month on average, along with increases in sexual desire, arousal, orgasm, sexual responsiveness, and a reduction in a women's distress from sexual dysfunction. Risks=no long-term data > 2 yr, no evidence in women with high cardiovascular disease or breast cancer, increase cholesterol level, dose for women not manufactured and usually requires compound. Not recommended for off-label uses like improving mood, cognition, or general well-being.[Global Consensus 2019]

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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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Health Canada May 2006: The **RUTH** study demonstrated an **increase in mortality due to stroke** for Evista compared to placebo. The incidence of stroke mortality was 1.5 per 1,000 women per year for placebo versus 2.2 per 1,000 women per year for Evista (p=0.0499). The incidence of stroke, myocardial infarction, hospitalized acute coronary syndrome, cardiovascular mortality, or overall mortality (all causes combined) was comparable for Evista and placebo. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/evista_hpc-cps_e.html Barrett-Connor E, et al.; Raloxifene Use for The Heart (**RUTH**) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N=10,101 5.6yrs N Engl J Med. 2006 Jul 13;355(2):125-37. (InfoPOEMs: For every 1000 women who take raloxifene for 5 years, we can expect 4 to 5 additional strokes, 6 additional episodes of venous thromboembolism (VTE), 6 fewer invasive breast cancers, and 6 to 7 fewer clinical vertebral fractures. The cost for this mixed bag of benefits and harms would be approximately $1000 per woman per year, for a total cost of $5,000,000 at current drug prices. (LOE = 1b))

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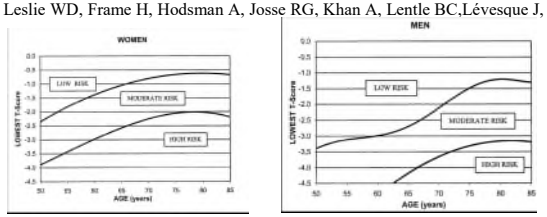

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ADHD Chart

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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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Metabolism of Benzodiazepines:

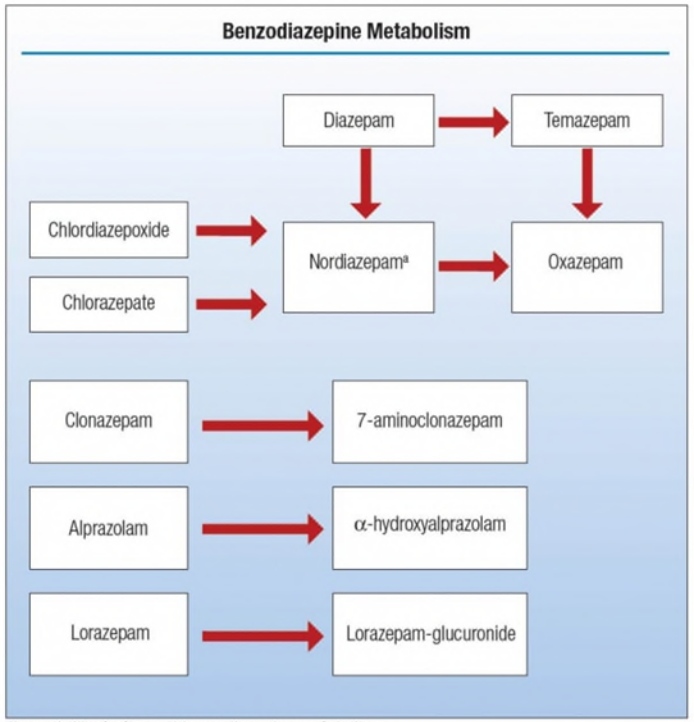

Figure 1: Illustrations of benzodiazepine metabolism.
Arrows indicate metabolic pathways
[a]Nordiazepam is also a metabolite of halazepam, medazepam, prazepam, and tetrazepam

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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**.

FDA Sep/17 is advising that the opioid addiction medications **buprenorphine and methadone** should not be withheld from patients taking **benzodiazepines** or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction usually outweighs these risks.

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

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.

Health Canada Jan/18 is advising Canadians and healthcare professionals that new safety warnings will be added to the product safety information of the following sedative and anesthetic drugs when they are used in early childhood and during pregnancy: Diprivan (propofol), Ketalar (ketamine), Sevorane (sevoflurane), Suprane (desflurane), Forane/Isoflurane USP (isoflurane), **Ativan (lorazepam), midazolam**, phenobarbital and thiopental. The safety review for benzodiazepines (Ativan [lorazepam] and midazolam) and barbiturates (phenobarbital and thiopental) concluded that there is limited evidence linking the use of these drugs by pregnant women and young children to adverse effects on the development of children's brains. However, it is important to note that many of these sedatives may often be used in combination with other intravenous and inhaled anesthetics, which were found to have a risk of adverse effects related to the functioning of the brain.

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Bipolar Disorder: Online Extras

Previously Used Agents:

Gabapentin ↓dose CrCl<60 **NEURONTIN**g (100,300,400 cap) (600ᶜ,800ᶜmg tab) ▼ 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	√seizures; Option:Neuropathic pain &**Anxiolytic in severe PD& social** **little effect as mood stabilizer** ↓ renal 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	19 32 **36** 42
Topiramate **TOPAMAX**g (25,50ˣ,100,200mg tab; 15, 25mg sprinkle cap) Hypospadias in male infants. Cleft lip/palate.	**Common**: nausea, dizzy, tremor, ataxia, somnolence, **cognitive dysfx**, headache, paresthesias, sedation, fatigue, diarrhea, metabolic acidosis, **nephrolithiasis & glaucoma** acute angle, stop tx! **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	62 114 **108** 154 154

Caution: ↓ **sweating** especially in children

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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
Health Canada Jan/10 is advising consumers not to use any unauthorized health products sold under **Natural Choice Lithium Orotate**.
Health Canada Feb/14 is informing health professionals and patients of new safety information and treatment recommendations regarding the drug **lithium** and the risks of high blood calcium (hypercalcemia) sometimes associated with a hormone disorder known as hyperparathyroidism.
Health Canada Dec/16 is advising Canadians that three unauthorized products, "**Lithium Plus, Serotonin Support, and Brain Support**," may pose serious health risks because they may contain Lithium Orotate.
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5HT=serotonin **ACh**=anticholinergic effects (dry mouth,constipation,urinary hesitancy,blurred vision) **ADHD**=attention deficit hyperactivity disorder **BP**=blood pressure **Cp**=plasma level avail **DA**=dopamine **D/C**=discontinuation **epi**=epinephrine **FT**=family therapy **IBS**=irritable bowel syndrome **IPT**=interpersonal therapy **MAOI**=monoamine oxidase inhibitors **MDD**=major depressive dx **NaSSA**=Noradrenergic/Specific Serotonergic Antidepressant **NDRI**=Norepinephrine Dopamine Reuptake⊖ **NE**=norepinephrine **OCD**=obsessive compulsive dx **RIMA**=reversible MAO-A⊖ **SARI**=Serotonin-2 Antagonist Reuptake⊖ **SED**=sedation **SSRI**=selective 5HT reuptake⊖ **TCA**=tricyclic antidepressant **↓**=initial dose lower than usual effective dose.

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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Antidepressants and the Risk of Acute Mocardial Infarction

- Serotonin plays a role in promoting the platelet aggregation.
- Antidepressants vary considerably in their mechanism of action and, consequently, they may show a different effect on the atherothrombotic risk.
- **Clomipramine** (a tricyclic antidepressant with a prominent selectivity on serotonin transporter) and **trazodone** (an antagonist of 5-HT2A receptor, which mediates the action of serotonin in platelets) were associated with a **decreased risk of AMI**, while other antidepressants showed no benefit.
- This study suggests that current use of antidepressants interfering selectively with the reuptake of serotonin, and those antagonizing the 5-HT2A receptor, are associated with a decrease in AMI risk and should be the antidepressants of choice in patients at cardiovascular risk.

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Post-Partum Depression – Effects of Antidepressants on Lactation & Breastfed Infants **Great references – enlarge to view details*

Reference: Beyond the baby blues: How pharmacists can help women struggling with postpartum depression
WRITTEN BY MILES LUKE, BAHAR NEMATI & LISA MCCARTHY ON MAY 10, 2020 FOR PHARMACY PRACTICE + BUSINESS

TABLE 2

EFFECTS OF MATERNAL ANTIDEPRESSANT USE ON LACTATION AND BREASTFED INFANTS

Medication	Relative infant dose (RID)*	Infant plasma concentration	Effects in breastfed infants	Effect on lactation	Additional considerations
Selective serotonin reuptake inhibitors (SSRIs)					
Citalopram	3%–10%, possibly higher[22,23]	<10% of maternal levels[30]	Colic, decreased feeding, irritability/restlessness[23] Normal body weight and neurological development at one year[25]	May cause galactorrhea or hyperprolactinemia; this may not affect lactation[23,27]	
Escitalopram	< 4%[23,30]	1.7% of maternal levels[30]	Normal infant development at 55 days.[30] Reversible sleepiness has been reported.[31]	May result in a small delay in lactogenesis (up to postpartum day 4)[28]	
Fluoxetine	3%–12% (fluoxetine + norfluoxetine) Norfluoxetine is an equally active metabolite.[33]	Sometimes > 10% for both fluoxetine and norfluoxetine.[32,33] Levels decrease after age 2 months.[30]	No neurological abnormalities at one year.[34] Normal weight gain can be expected.[35,36]		Due to observed RIDs > 10% and the prolonged half-life of fluoxetine, alternate agents may be preferred when starting antidepressant therapy in a breastfeeding mother.[32,33]
Fluvoxamine	1%[33]	Generally undetectable[38]	Normal weight gain and no adverse effects[38]		
Paroxetine	1%–2%[33]	Undetectable[33,34]	Normal weight gain[39] Uncommon: restlessness, insomnia, increased crying.[34]		Paroxetine may be preferred antidepressant in the treatment of PPD in women who are breastfeeding, due to rare adverse effects and low levels in breast milk and infant serum.[14,40] Maternal use of paroxetine during the first trimester may increase risk of fetal cardiac malformations. If the breastfeeding mother is considering subsequent pregnancies, then alternate agents may be preferred for the treatment of PPD.[17,31]
Sertraline	0.5%[22,42]	Generally low or undetectable, but rare cases of up to 15%[42]	Normal weight gain and no adverse effects[22,38,42]		A preferred antidepressant in the treatment of PPD in women who are breastfeeding, due to no adverse effects and low levels in breast milk and infant serum.[17]
Serotonin–norepinephrine reuptake inhibitors (SNRIs)					
Desvenlafaxine	6.8%[43]	4.8%–5.8%[43]	Short-term exposure (average = 9 days) associated with decreased growth, but normal development and no acute adverse effects.[43]	May cause galactorrhea or hyperprolactinemia, but may not affect lactation.[44–46]	Total infant drug exposure is less with mothers taking desvenlafaxine than with mothers taking venlafaxine.[43]
Duloxetine	< 1%[47,48]	Undetectable or very low levels[48,50]	Normal development at 6 months and no adverse effects reported in two case reports.[48]	May result in a small delay in lactogenesis (up to postpartum day 4).[51]	
Venlafaxine	5.2%–7.4% (venlafaxine + desvenlafaxine).[52,53] Desvenlafaxine is an equally active metabolite[51]	Venlafaxine generally undetectable Desvenlafaxine usually present in small amounts[52,53]	No adverse effects reported.[52,53]		
Serotonin modulators					
Vortioxetine	No literature published				
Norepinephrine–dopamine reuptake inhibitor (NDRI)					
Bupropion	5.7%[55]	Undetectable[55]	Two case reports of seizures[54,55]	May cause an increase in prolactin levels and galactorrhea, but has not been shown to affect lactation.[56]	Agents other than bupropion may be preferred for breastfeeding mothers, due to case reports of seizures in breastfed infants.[57]
Alpha$_2$-adrenergic agonist/5-HT$_3$ antagonist					
Mirtazapine	1.5%[58]	Undetectable[58]	No adverse effects reported[59]	May cause an increase in prolactin levels, but not shown to affect lactation.[60]	

PPD=postpartum depression; *RID=relative infant dose (defined as the weight-adjusted amount of drug in breast milk that the infant ingests, expressed as a percentage of the weight-adjusted maternal dose. RID < 10% is usually considered clinically unimportant)

TABLE 3[60-64]

CONSIDERATIONS WHEN EVALUATING THE SAFETY OF MEDICATIONS FOR USE DURING BREASTFEEDING AND LACTATION

Transfer into breast milk

Drugs that are lipophilic, have low molecular weight (< 800 Da), small volume of distribution (< 1 L/kg), or are not highly protein-bound (< 90%) pass relatively freely into breast milk.[60]

Weakly basic drugs with pKa > 7.2 become ionized in breast milk and do not diffuse back into maternal serum.[60,61]

Relative infant dose (RID) is the weight-adjusted amount of drug in breast milk that the infant ingests, expressed as a percentage of the weight-adjusted maternal dose.[60,62]

RID < 10% is usually considered clinically unimportant.[62]

Drugs that have severe toxicities (e.g., chemotherapy, gold) are contraindicated in breastfeeding even if RID < 10%.[60]

Risk of adverse effects to infant

Infants rarely experience adverse effects after exposure to medications via breast milk.[61,62]

Infants are at greatest risk of adverse effects at ages < 6 months.[63]

Drugs with low oral bioavailability and/or enteric coating pose little risk to breastfed infants because they are not readily absorbed from the infant's gastrointestinal tract.[61]

Drug concentration in breast milk is proportional to the concentration in maternal plasma; infant exposure may be limited by avoiding breastfeeding around the time of peak plasma concentration.[60]

Drugs with shorter half-lives allow for more frequent breastfeeding while at trough plasma concentrations.[60,62]

Effects on lactation

Drugs can affect lactogenesis when given perinatally or alter lactation after it has been established.[64]

Drugs with dopaminergic activity may decrease maternal serum prolactin concentrations, which can suppress lactation.[64]

Estrogens, androgens and drugs with anticholinergic or sympathomimetic properties may suppress lactation.[64]

Drugs that impair oxytocin secretion may reduce milk ejection.[64]

Antidepressant	**185**
Depression	**185**
Drug-Induced Depression	185
MAOI	185
Serotonin Syndrome	185
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SSRI	185
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Withdrawal Syndrome	185
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ANAFRANIL	**186**
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AVENTYL	**186**
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Bupropion	**186**
CELEXA	**186**
CIPRALEX	**186**
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Clomipramine	**186**
CYMBALTA	**186**
Depression	**186**
Desipramine	**186**
Desvenlafaxine	186
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Doxepin	**186**
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EFFEXOR	**186**
ELAVIL	**186**
Escitalopram	**186**
Esketamine	186
FETZIMA	186
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Fluvoxamine	**186**
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Levomilnacipran	186
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Mirtazapine	**186**
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ANTIDEPRESSANT COMPARISON CHART - References

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Sept/05 Nice:Depression in children & young people http://www.nice.org.uk/pdf/CG028NICEguideline.pdf ; (Simon GE, Savarino J, Operskalski B, Wang PS. **Suicide risk during antidepressant treatment**. Am J Psychiatry. 2006 Jan;163(1):41-7. CONCLUSIONS: The risk of suicide during acute-phase antidepressant treatment is approximately one in 3,000 treatment episodes, and risk of serious suicide attempt is approximately one in 1,000. Available data do not indicate a significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs.)(Cheung AH, et al. The use of antidepressants to treat depression in children and adolescents. CMAJ. 2006 Jan 17;174(2):193-200.) & (Hammad TA, et al. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006 Mar;63(3):332-9. CONCLUSION: Use of antidepressant drugs in pediatric patients is associated with a modestly increased risk of suicidality. InfoPOEMs: The use of antidepressant medications in children is associated with an increased risk of suicidal ideation and suicide-related behaviors. It is uncertain what overall effect antidepressant medications have on the morbidity and mortality of treated children. Close monitoring of patients using these medications regarding the risk of suicidality is recommended. (LOE = 1a-)) (Glaxo May/06 Meta analysis: 8958 paroxetine & 5953 placebo pts; suicidal behavior aged 18-24yrs (2.19 vs 0.92%); all ages (0.32 vs 0.05%); all were nonfatal suicide attempts; 8 of 11 attempts were in aged 18-30yrs) Emslie GJ, et al. Paroxetine Treatment in Children and Adolescents With Major Depressive Disorder: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial. J Am Acad Child Adolesc Psychiatry. 2006 Jun;45(6):709-719. Paroxetine was not shown to be more efficacious than placebo for treating pediatric major depressive disorder. (Misri S, et al. Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications. Am J Psychiatry. 2006 Jun;163(6):1026-32.) (Dubicka B, Hadley S, Roberts C. **Suicidal** behaviour in youths with depression treated with new-generation antidepressants: meta-analysis. Br J Psychiatry. 2006 Nov;189:393-8. Self-harm or suicide-related events occurred in 71 of 1487 (4.8%) of depressed youths treated with antidepressants v. 38 of 1254 (3.0%) of those given placebo (fixed effects odds ratio 1.70, 95% CI 1.13-2.54, P=0.01).) (Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant prescription rates and rate of early adolescent **suicide**. Am J Psychiatry. 2006 Nov;163(11):1898-904. The aggregate nature of these observational data precludes a direct causal interpretation of the results. More SSRI prescriptions are associated with lower suicide rates in children and may reflect antidepressant efficacy, treatment compliance, better quality mental health care, and low toxicity in the event of a suicide attempt by overdose.) (Juurlink DN, et al. The risk of **suicide** with selective serotonin reuptake inhibitors in the **elderly**. Am J Psychiatry. 2006 May;163(5):813-21. Initiation of SSRI therapy is associated with an increased risk of suicide during the first month of therapy compared with other antidepressants. The absolute risk is low, suggesting that an idiosyncratic response to these agents may provoke suicide in a vulnerable subgroup of patients.) (Olfson M, Marcus SC, Shaffer D. Antidepressant drug therapy and **suicide** in severely depressed children and adults: A case-control study. Arch Gen Psychiatry. 2006 Aug;63(8):865-72. In these high-risk patients, antidepressant drug treatment does not seem to be related to suicide attempts and death in adults but might be related in children and adolescents. These findings support careful clinical monitoring during antidepressant drug treatment of severely depressed young people.) (Tiihonen J, et al. Antidepressants and the risk of **suicide**, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry. 2006 Dec;63(12):1358-67. Among suicidal subjects who had ever used antidepressants, the current use of any antidepressant was associated with a markedly increased risk of attempted suicide and, at the same time, with a markedly decreased risk of completed suicide and death. Lower mortality was attributable to a decrease in cardiovascular- and cerebrovascular-related deaths during selective serotonin reuptake inhibitor use.) (Simon GE. The antidepressant quandary--considering suicide risk when treating adolescent depression. N Engl J Med. 2006 Dec 28;355(26):2722-3.)
(Bhatia SK, Bhatia SC. Childhood and adolescent depression. Am Fam Physician. 2007 Jan 1;75(1):73-80.) (Bridge JA, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled rials. JAMA. 2007 Apr 18;297(15):1683-96. Relative to placebo, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. Benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.) (Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Mann JJ. Relationship between antidepressants and suicide attempts: an analysis of the veterans health administration data sets. Am J Psychiatry. 2007 Jul;164(7):1044-9. These findings suggest that SSRI treatment has a **protective effect** in all adult age groups. They do not support the hypothesis that SSRI treatment places patients at greater risk of suicide.)
Gibbons RD, Brown CH, Hur K, et al. Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents. Am J Psychiatry. 2007 Sep;164(9):1356-63. In both the United States and the Netherlands, SSRI prescriptions for children and adolescents decreased after U.S. and European regulatory agencies issued warnings about a possible suicide risk with antidepressant use in pediatric patients, and these decreases were associated with increases in suicide rates in children and adolescents.
Hetrick S, Merry S, McKenzie J, Sindahl P, Proctor M. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. **Cochrane** Database Syst Rev. 2007 Jul 18;(3):CD004851. There was also evidence of an increased risk of suicidal ideation and behaviour for those prescribed SSRIs (RR 1.80, 95% CI 1.19 to 2.72). Fluoxetine was the only SSRI where there was consistent evidence from three trials that it was effective in reducing depression symptoms in both children and adolescents (CDRS-R treatment effect -5.63, 95% CI -7.38 to -3.88), and 'response' to treatment (RR 1.86, 95% CI 1.49 to 2.32). Where rates of adverse events were reported, this was higher for those prescribed SSRIs. While untreated depression is associated with the risk of completed suicide and impacts on functioning, it is unclear whether SSRIs would modify this risk in a clinically meaningful way. (Cheung AH, Zuckerbrot RA, Jensen PS, Ghalib K, Laraque D, Stein RE; GLAD-PC Steering Group. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): II. Treatment and ongoing management. Pediatrics. 2007 Nov;120(5):e1313-26.)
Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the **TORDIA** randomized controlled trial.JAMA. 2008 Feb 27;299(8):901-13. For adolescents with depression not responding to an adequate initial treatment with an SSRI, the combination of cognitive behavioral therapy and a switch to another antidepressant resulted in a higher rate of clinical response than did a medication switch alone. However, a switch to another SSRI was just as efficacious as a switch to venlafaxine and resulted in fewer adverse effects.
Tsapakis EM, et al. Efficacy of antidepressants in juvenile depression: **meta-analysis**.. Br J Psychiatry. 2008 July:193;10-17. Antidepressants of all types showed limited efficacy in juvenile depression, but fluoxetine might be more effective, especially in adolescents. Studies in children & in severely depressed, hospitalised or suicidal juvenile patients are needed, and effective, safe and readily accessible treatments for juvenile depression are urgently required. This meta-analysis found that selective serotonin reuptake inhibitors (SSRIs) -- fluoxetine, in particular -- are modestly effective for depression in adolescents. Tricyclic antidepressants (TCAs) were not effective. Antidepressants were not effective in younger children. (LOE = 1a)
Wheeler BW, Gunnell D, Metcalfe C, Stephens P, Martin RM. The population impact on incidence of suicide and non-fatal self harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: ecological study. BMJ. 2008 Mar 8;336(7643):542-5. Epub 2008 Feb 14. The noticeable reduction in prescribing of antidepressants since regulatory action in 2003 to restrict the use of SSRIs in under 18s does not seem to have been associated with changes in suicidal behaviour in young people. Specifically, these data for England do not indicate that reductions in antidepressant use have led to an increase in suicidal behaviour.
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with depression. Among adolescents, use of SSRIs may increase suicidality.
Stone Marc, Laughren Thomas, Jones M Lisa, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ 2009;339:b2880, doi: 10.1136/bmj.b2880 (Published 11 August 2009) Findings showed eight completed suicides, 134 suicide attempts, 10 patients who had made preparations without attempting suicide, and 378 patients who had thoughts about suicide but had not acted on them. These results suggest that, compared with placebo, the risks of suicidality associated with antidepressants are strongly age dependent - the risk is **raised in people under 25**, not affected in those aged 25-64, and reduced in those aged 65 and older, say the authors.

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[31] Treatment for Adolescents with Depression Study (**TADS**). **Fluoxetine**, Cognitive-Behavioral Therapy, & their Combination for Adolescents with Depression. JAMA. 2004 Aug 18;292(7):807-820. (Kennard B, Silva S, Vitiello B, et al. TADS Team. Remission and residual symptoms after short-term treatment in the Treatment of Adolescents with Depression Study (TADS). J Am Acad Child Adolesc Psychiatry. 2006 Dec;45(12):1404-11. The combination of FLX and CBT was superior to both monotherapy and PBO in terms of remission rates, but overall rates of remission remain low and residual symptoms are common at the end of 12 weeks of treatment.) (March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. The Treatment for Adolescents With Depression Study (TADS): long-term effectiveness and safety outcomes. Arch Gen Psychiatry. 2007 Oct;64(10):1132-43. In adolescents with moderate to severe depression, treatment with fluoxetine alone or in combination with CBT accelerates the response. Adding CBT to medication enhances the safety of medication. Taking benefits & harms into account, combined treatment appears superior to either monotherapy as a treatment for major depression in adolescents.)
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Sharma T, Guski LS, Freund N, et al. **Suicidality and aggression** during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ 2016;352:i65. (especially in kids & adolescents)

[33] Paxil (Paroxetine) and Birth Defects Pharmacist's Letter October 2005. (First trimester: Paxil any malformations 4% vs ~3% general population; cardiac 2% vs ~1% general population ; most common cardiac malformation was ventricular septal defects) See also: Hallberg P, Sjoblom V. The use of selective serotonin reuptake inhibitors during pregnancy and breast-feeding: a review and clinical aspects. J Clin Psychopharmacol. 2005 Feb;25(1):59-73. & Health Canada warning Oct/05 http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/paxil_3_hpc-cps_e.pdf (Preliminay report of retrospective epidemiological study of 3,581 pregnant women). Dec/05 Health Canada update http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/paxil_4_hpc-cps_e.html (An independent epidemiological study of delivery outcome following maternal use of SSRI antidepressants in early pregnancy has been conducted utilizing the Swedish national registry data (n=5,123 women). The findings show an approximate 2-fold increased risk of cardiac malformations in infants exposed to paroxetine, compared with the total registry population (approximately 2% incidence vs. 1%, respectively).) (Use of SSRIs During Pregnancy Pharmacist's Letter April 2006) (**ACOG** Publications: Committee Opinion No. 354: Treatment With **Selective Serotonin Reuptake Inhibitors** During **Pregnancy** Obstet Gynecol 2006 108: 1601-1604.) (Djulus J, Koren G, et al. Exposure to **Mirtazapine** During **Pregnancy**: A Prospective, Comparative Study of Birth Outcomes. J Clin Psychiatry. 2006 Aug;67(8):1280-1284. Mirtazapine does not appear to increase the baseline rate of major malformations of 1% to 3%. However, the higher number of spontaneous abortions in the antidepressant groups confirms the higher rates of spontaneous abortions in pregnant women taking antidepressant medications found in previous studies.) (Kristensen JH, et al. Transfer of the antidepressant **mirtazapine** into **breast milk**. Br J Clin Pharmacol. 2006 Sep 13; [Epub ahead of print] Results Mean (95% confidence interval) relative infant doses for mirtazapine and desmethylmirtazapine (n = 8) were 1.5% (0.8, 2.2) and 0.4% (0.2, 0.6) respectively.) (Thormahlen GM. **Paroxetine** Use During **Pregnancy**: Is it Safe? (October). Ann Pharmacother. 2006 Aug 22; [Epub ahead of print]) (Wogelius P, et al. Maternal Use of Selective **Serotonin Reuptake Inhibitors** and Risk of **Congenital Malformations**. Epidemiology. 2006 Nov;17(6):701-704. The 150,780 women with no SSRI prescriptions gave birth to 5112 (3.4%) children with congenital malformations. The 1051 women with SSRI prescriptions any time during early pregnancy gave birth to 51 (4.9%) children with congenital malformations.)
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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
Health Canada Apr/19: **BENLYSTA (belimumab**) - Increased Risk of Serious Depression, Suicidal Ideation or Behaviour, or Self-Injury.
Health Canada Apr/19: Apotex Inc. is recalling one lot (lot RF0410, expiry 05/2024) of APO-Amitriptyline 10 mg tablets after testing identified levels of N-nitrosodimethylamine (NDMA) above what is considered acceptable if the drug were to be taken over a lifetime.
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nefazodone[3A4] SERZONE[FDA only]	carbamazepine ⑥⑨ cisapride ②[cv] ⑥ lovastatin ⑥[rhabdo] MAOIs 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 ⑥ ⑨	**pimozide** ⑥[cv] pravastatin ⑥ quinidine ② ⑥	ritonavir ⑧ **sedatives** ① tacrolimus ②⑥	triazolam ⑥

CNS=central nervous system **CV**=cardiovascular **HTN**=hypertension

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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 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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prematurely discharged from care, if triage relies on the presence of FRS to diagnose schizophrenia. Empathetic, considerate use of FRS as a diagnostic aid - with known limitations - should avoid a good proportion of these errors. We hope that newer tests - to be included in future
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SLEEP/INSOMNIA

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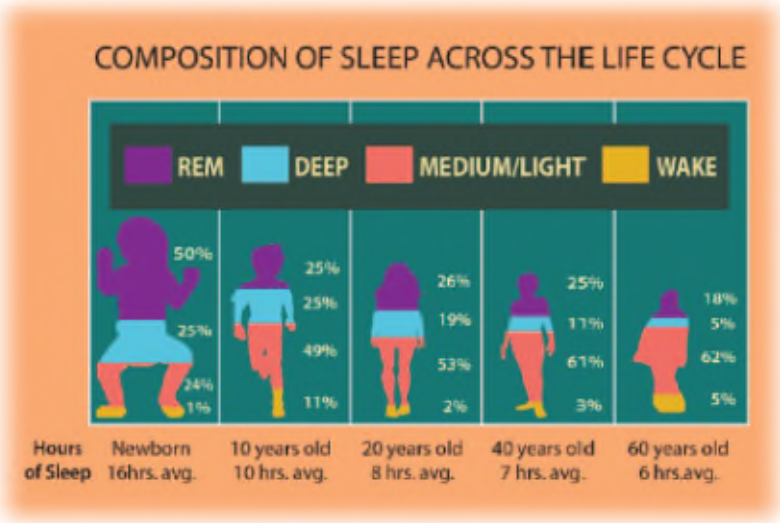
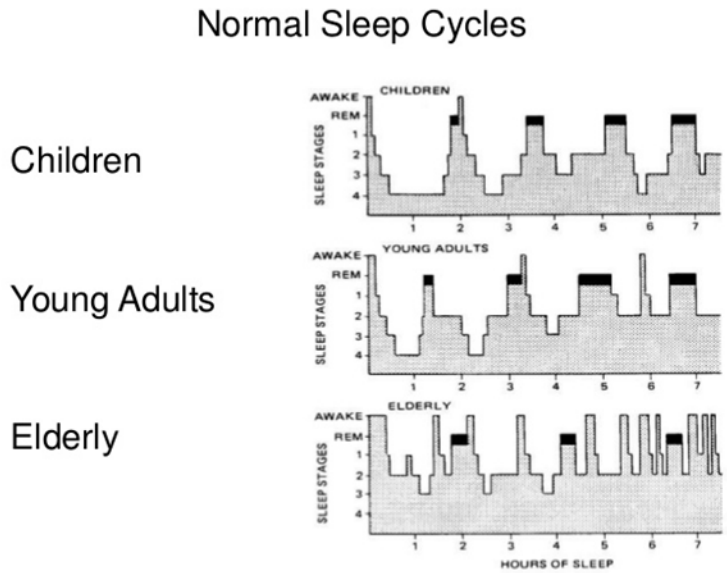
Useful Links
Epworth Sleepiness Scale: Score 0-10: Normal Daytime Sleepiness, Score >10: Excessive Daytime Sleepiness http://epworthsleepinessscale.com/about-the-ess/
Resource for Self Help: Silberman, Stephanie. The Insomnia Workbook. A Comprehensive Guide to Getting the Sleep You Need. New Harbinger Publications, Inc. 2009.
Management of Chronic Insomnia – Support Tool (Centre for Effective Practice, Toronto): cep.health/clinical-products/insomnia-management-of-chronic-insomnia-tool
Online Canadian Resources - https://mysleepwell.ca/ (Nova Scotia), http://sinkintosleep.com/, https://drcolleencarney.com/, **Kelty's Key:** Insomnia (British Columbia), BC PAD Insomnia Handout.
Drug and Alcohol Services South Australia Insomnia Management Kit: Stimulus Control Therapy, Bedtime Restriction Therapy

Figure 1: Composite of Sleep Across the Life Cycle[Driver 2012]





Shift worker recommendations[Wallace 2020]

Personal	Institution driven policies or breaks
Nap prior to shift	Nap for 20-30 mins during shift between 0200 and 0300 am {lowest level of performance after 0400am}.
Caffeine 4mg/kg early in the shift increases performance; not be consumed within 4 hours of the end of shift to minimize any effects on sleep immediately following work.	Bright light exposure on shift (blue wavelength, 4000 to 12,000 lux).
Consume multiple small healthy snacks as opposed to 1 large meal.	Reduce length and number of consecutive night shifts.
Use dark lensed sunglasses on commute home.	Schedules should follow a clockwise rotation (morning, afternoon, then night).
Melatonin 5-10mg may reduce sleep onset latency and increase total sleep length.	Avoid extending shifts or scheduling duties after night shifts.
Use blackout curtains or a sleeping mask.	Minimize the magnitude and frequency of transitions to and from night shift.
Maintain a cold sleeping environment during the day with a warm water bottle at the feet.	Allow providers control over their schedule by selecting their own night shift (more satisfaction, less stress, less fatigue).

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SEDATIVE COMPARISON CHART

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patients with insomnia, right? It's too simple, cheap, and uses no medications. Oops, I guess I was wrong. My biggest concern with this study is that primary insomnia is not all that common and the authors didn't study whether this could work in patients with secondary sleep disorders.
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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.
FDA Dec/16 is warning that repeated or lengthy use of **general anesthetic and sedation drugs during surgeries or procedures** in **children younger than 3 years or in pregnant women** during their third trimester **may affect the development of children's brains**.
FDA Apr/19: is advising that rare but serious injuries have happened with certain common prescription insomnia medicines because of sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors have also resulted in deaths. These behaviors appear to be more common with **Lunesta (eszopiclone), Sonata (zaleplon), Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist (zolpidem)** than other prescription medicines used for sleep. https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia
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Health Canada Dec/06 is advising consumers not to use a product called **Eden Herbal Formulations Sleep Ease Dietary Supplement**, because it was found to contain an undeclared drug estazolam http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_127_e.html
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.
Health Canada May/17 is advising Canadians that multiple unauthorized products labelled to contain **L-tryptophan** or lithium orotate were being sold on amazon.ca, and may pose serious health risks.
Health Canada Jan/18 is advising Canadians and healthcare professionals that new safety warnings will be added to the product safety information of the following **sedative and anesthetic drugs** when they are used in early childhood and during pregnancy: Diprivan (propofol), Ketalar (ketamine), Sevorane (sevoflurane), Suprane (desflurane), Forane/Isoflurane USP (isoflurane), Ativan (lorazepam), midazolam, phenobarbital and thiopental. The safety review for benzodiazepines (Ativan [lorazepam] and midazolam) and barbiturates (phenobarbital and thiopental) concluded that there is limited evidence linking the use of these drugs by pregnant women and young children to adverse effects on the development of children's brains. However, it is important to note that many of these sedatives may often be used in combination with other intravenous and inhaled anesthetics, which were found to have a risk of adverse effects related to the functioning of the brain.
Health Canada Dec/19 is advising Canadians that it has tested several **U-Dream Lite and U-Dream Full Night** herbal sleep-aid products and has found that they contain a substance similar to the prescription drug zopiclone, which may pose serious health risks.
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Web Sites:
National Heart Lung and Blood Institute http://www.nhlbi.nih.gov/health/dci/Diseases/inso/inso_whatis.html
American Academy of Sleep Medicine www.sleepeducation.com

Background Info:

Medication "targets" or MOAs

- BZs & Z-Drugs → $GABA_A$ receptor, but on different receptor subunits
- Antihistamines (doxepin, diphenhydramine, doxylamine) → histamine receptor
- Melatonin, ramelteon, tasimelteon, piromelatine → act on the melatonin system

Orexins (aka hypocretins)
Suvorexant → The orexin neuropeptide signaling system is a central promoter of wakefulness. Orexin-producing neuronal cell bodies are localized specifically in the hypothalamus and project to the wakefulness mediating neurons of the brain. Suvorexant is thought to suppress wake drive by blocking the binding of the wake-promoting neuropeptides orexin A and orexin B to OX1R and OX2R reversibly. Suvorexant has no direct pharmacological activity or binding affinity (Ki >10 µM) at gamma-aminobutyric acid (GABA), serotonin, dopamine, noradrenaline, melatonin, histamine, acetylcholine, or opiate receptors.

Feb 2020 – Phase III trial Phase – Daridorexant →dual orexin receptor antagonist – indication: insomnia disorder
Good study looking at efficacy for when daridorexant comes to market: https://www.ncbi.nlm.nih.gov/pubmed/31953863

Lemborexant – article for when it's approved in Canada and more details about the efficacy is desired: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2758000

Non-Rx Meds (from Pharmacy Practice Jan/Feb 2020)

Melatonin

- Modest reduction in time to sleep, may improve quality of sleep
- Strongest clinical evidence for use in delayed phase sleep disorder and jet lag

Valerian Extract

- May have positive effects on sleep (better quality evidence required)
- Safety of long-term use has not been studied

Diphenhydramine

- Small reduction in time to sleep and total sleep time at doses of 50mg daily for 2-4 weeks
- Efficacy and safety for long-term use is not well established
- Use with caution in older adults and patients with significant medical comorbidities due to anticholinergic side-effect profile

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Asthma Clinical Controversies	
In mild asthma, should prn SABA therapy be abandoned in favour of a prn LABA/ICS?	This approach would be supported by some new guidelines (e.g. GINA 2019). Evidence is based on the **SYGMA1** and **Novel START** trials. The rationale is it prevents patients from becoming accidentally dependent on SABA monotherapy, & LABA/ICS therapy reduces exacerbations compared to SABA prn therapy (e.g. in **SYGMA1**, 11.9% of patients had an asthma exacerbation on prn SABA therapy, compared to 5.6% of patients on prn LABA/ICS and 6.1% of patients on daily ICS). However, it is important to note that: • Patients in the **Novel START** trial used a SABA on average 7 times per week, and exacerbations were common. In real-life practice, this level of SABA use would be a signal for stepping up to an ICS. In other words, patients with asthma who only use a SABA 2 times per week may still be good candidates to continue SABA monotherapy, and patients using a SABA regularly may be better off stepping up to a scheduled ICS rather than using a prn LABA/ICS (see next question below). • Overusing a SABA may increase the risk of death. However, this risk seems to appear when more than 200 doses of SABA (i.e. more than 1 cannister) are used per month.[24]
In mild asthma, should scheduled inhaled steroid therapy be abandoned in favour of a prn LABA/ICS?	Similar to the above, this approach is also supported by some new guidelines (e.g. GINA 2019). The rational is it may result in less overall steroid exposure but with a similar rate of exacerbations, while increasing patient convenience & adherence. Evidence is based on the **PRACTICAL**, **SYGMA 1**, and **SYGMA 2** trials. However, it is important to note that: • In the **SYGMA 1** and **SYGMA 2** trials, prn LABA/ICS resulted in overall less well-controlled asthma versus a scheduled ICS (e.g. about 5 less weeks per year of well-controlled asthma).[21] Thus ICS monotherapy, especially with an added **action plan**, is still a good choice for many patients.
Note that if a prn LABA/ICS approach is chosen, a **fast-onset LABA** (e.g. formoterol) should be used.	

Search Terms:

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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.

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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 budesonide and beclomethasone. Clinicians should carefully weigh the potential benefits and harm of each treatment option, taking into account the unknown long-term (> one year) impact of intermittent therapy on lung growth and lung function decline.

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, sue 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.

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FDA Mar/15 is warning consumers **not** to rely on asthma products labeled as **homeopathic** that are sold over-the-counter (OTC). These products have not been evaluated by the FDA for safety and effectiveness.

FDA Dec/17: most prominent warning, the **Boxed Warning**, about asthma-related death has been **removed from the drug labels of medicines that contain both an ICS and LABA**. A FDA review of four large clinical safety trials shows that treating asthma with long-acting beta agonists (LABAs) in combination with inhaled corticosteroids (ICS) does not result in significantly more serious asthma-related side effects than treatment with ICS alone. A description of the four trials is now also included in the Warnings and Precautions section of the drug labels. These trials showed that LABAs, when used with ICS, did not significantly increase the risk of asthma-related hospitalizations, the need to insert a breathing tube known as intubation, or asthma-related deaths, compared to ICS alone.

FDA Mar/20: is strengthening existing warnings about serious **behavior and mood-related changes with montelukast** (Singulair; Merck and generics), which is used to treat asthma and allergy. The agency will add a boxed warning to montelukast advising healthcare providers to avoid prescribing montelukast for patients with mild symptoms, particularly those with allergic rhinitis, according to a drug safety communication.

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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
Health Canada May/17: **Placebo tablets** by Australia Therapeutic Goods Administration has undeclared **clenbuterol**.
Health Canada Feb/18: is advising Canadians that GlaxoSmithKline Inc. is voluntarily **recalling** one lot of **Ventolin Diskus inhalers** (lot 786G) because the products may not deliver the intended dose. Individuals who do not receive the intended dose may not be aware that the dose was not delivered.
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Kapur N, Petsky HL, Bell S, Kolbe J, Chang AB. **Inhaled corticosteroids for bronchiectasis**. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD000996. This updated review indicates that there is insufficient evidence to suppor t the routine use of ICS in adults with stable state bronchiectasis. Further, we cannot draw any conclusion for the use of ICS in adults during an acute exacerbation or in children (for any state), as there were no studies.

Karaca-Mandic P, Jena AB, Joyce GF, Goldman DP. **Out-of-pocket medication costs** and use of medications and health care services among children with asthma. JAMA. 2012;307(12):1284-1291.

Karner C, Cates CJ. The effect of **adding inhaled corticosteroids to tiotropium and long-acting beta(2)-agonists for chronic obstructive pulmonary disease**. Cochrane Database Syst Rev. 2011 Sep 7;9:CD009039. The relative efficacy and safety of adding inhaled corticosteroid to tiotropium and a long-acting beta(2)-agonist for chronic obstructive pulmonary disease patients remains uncertain and additional trials are required to answer this question.

Karner C, Cates CJ. **Long-acting beta(2)-agonist in addition to tiotropium** versus either tiotropium or long-acting beta(2)-agonist alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012 Apr 18;4:CD008989. The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and long-acting beta(2)-agonist compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. Hospital admission and mortality have not been shown to be altered by adding long-acting beta(2)-agonists to tiotropium. There were not enough data to determine the relative efficacy and safety of tiotropium plus long-acting beta(2)-agonist compared to long-acting beta(2)-agonist alone. There were insufficient data to make comparisons between the different long-acting beta(2)-agonists when used in addition to tiotropium.

Karner C, Cates CJ. Combination inhaled steroid and long-acting beta(2)-agonist in addition to **tiotropium versus tiotropium or combination** alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2011 Mar 16;(3):CD008532.

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.

Karvonen AM, Hyvärinen A, Korppi M, et. al, **Moisture Damage and Asthma**: A Birth Cohort Study. Pediatrics. 2015 Feb 16. pii: peds.2014-1239. [Epub ahead of print] PubMed PMID: 25687143.

Katzka DA. **Eosinophilic Esophagitis**. Ann Intern Med. 2020 May 5;172(9):ITC65-ITC80

Kawasumi Y, et al. **Comparative Effectiveness of Tiotropium and Ipratropium** in Prevention of Hospital Readmission for COPD: Population-Based Cohort Study. Clin Ther. 2013 Mar 12.

Keeney GE, Gray MP, Morrison AK, et al. **Dexamethasone for Acute Asthma** Exacerbations in Children: A Meta-analysis. Pediatrics. 2014 Feb 10.

Keet CA, McCormack MC, et al. **Neighborhood poverty, urban residence, race/ethnicity, and asthma**: Rethinking inner-city asthma epidemic. J Allergy Clin Immunol. 2015 Jan 7.

Keet CA, Keller JP, Peng RD. **Long-term Coarse PM Exposure** is Associated with Asthma Among Children in Medicaid. Am J Respir Crit Care Med. 2017 Dec 15.

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.

Kelly HW, Sternberg AL, Lescher R, et al; the **CAMP** Research Group. Effect of Inhaled Glucocorticoids in **Childhood on Adult Height**. N Engl J Med. 2012 Sep 3.

Kempsford R, Allen A, Bal J, et al. The effect of **ketoconazole** on the pharmacokinetics and pharmacodynamics of inhaled **fluticasone** furoate and **vilanterol** trifenatate in healthy

subjects. Br J Clin Pharmacol. 2012 Nov 1.

Kennedy S, Bailey R, Jaffee K, et al. **Effectiveness of Evidence-Based Asthma Interventions**. Pediatrics.2017;139(6):e20164221

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.

Kenyon CC, Rubin DM, Zorc JJ, et al. Childhood Asthma Hospital **Discharge Medication Fills and Risk of Subsequent Readmission**. J Pediatr. 2015 May;166(5):1121-7.

Kenyon CC, Strane D, Floyd GC, et al. An **Asthma Population Health Improvement Initiative** for Children With Frequent Hospitalizations. Pediatrics. 2020 Oct 1:e20193108

Kercsmar CM, Beck AF, Sauers-Ford H, et al. Association of an **asthma improvement collaborative** with health care utilization in Medicaid-insured pediatric patients in an urban community [online September 18, 2017]. *JAMA Pediatr*. doi:10.1001/jamapediatrics.2017.2600

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

Kerstjens HA, Disse B, Schroder-Babo W, et al. **Tiotropium** improves lung function in patients with severe uncontrolled **asthma**: a randomized controlled trial. J Allergy Clin Immunol. 2011 Aug;128(2):308-14.

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.

Kew KM, Carr R, Donovan T, et al. **Asthma education for school staff**. Cochrane Database Syst Rev. 2017 Apr 12;4:CD012255. Asthma education for school staff increases asthma knowledge and preparedness, but studies vary and all available evidence is of low quality. Studies have not yet captured whether this improvement in knowledge has led to appreciable benefits over the short term or the longer term for the safety and health of children with asthma in school. Randomised evidence does not contribute to our knowledge of content or attributes of interventions that lead to the best outcomes, or of resources required for successful implementation.Complete reporting of the content and resources of educational interventions is essential for assessment of their effectiveness and feasibility for implementation. This applies to both randomised and non-randomised studies, although the latter may be better placed to observe important clinical outcomes such as exacerbations and mortality in the longer term.

Kew KM, Malik P, Aniruddhan K, Normansell R. **Shared decision-making** for people with asthma. Cochrane Database Syst Rev. 2017 Oct 3;10:CD012330. Substantial differences between the four included randomised controlled trials (RCTs) indicate that we cannot provide meaningful overall conclusions. Individual studies demonstrated some benefits of SDM over control, in terms of quality of life; patient and parent satisfaction; adherence to prescribed medication; reduction in asthma-related healthcare visits; and improved asthma control. Our confidence in the findings of these individual studies ranges from moderate to very low, and it is important to note that studies did not measure or report adverse events.

Kher S, Mota P. **Maternal asthma**: Management strategies. Cleve Clin J Med. 2017 Apr;84(3):296-302.

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.

Khreis H, et al. Full-chain health impact assessment of **traffic-related air pollution and childhood asthma**. Environ Int 2018; online 27 Mar. https://doi.org/10.1016/j.envint.2018.03.008.

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 LHY, Saleh C, Whalen-Browne A, et al. **Triple vs Dual Inhaler Therapy** and Asthma Outcomes in Moderate to Severe Asthma: A Systematic Review and Meta-analysis. JAMA. 2021 May 19. doi: 10.1001/jama.2021.7872

Kim V, Criner GJ. **Chronic bronchitis and chronic obstructive pulmonary disease**. Am J Respir Crit Care Med. 2013 Feb 1;187(3):228-37.

Kim BS, Mehra S, Yawn B, et al. Increased Risk of **Herpes Zoster** in Children with Asthma: A Population-Based Case-Control Study. J Pediatr. 2013 Apr 13.

Kim JM, Lin SY, Suarez-Cuervo C, et al. **Allergen-Specific Immunotherapy** for Pediatric Asthma and Rhinoconjunctivitis: A Systematic Review. Pediatrics. 2013 May 6.

King-Biggs MB. **Asthma**. Ann Intern Med. 2019 Oct 1;171(7):ITC49-ITC64.

Kirkland SW, Vandenberghe C, Voaklander B, Nikel T, Campbell S, Rowe BH. **Combined inhaled beta-agonist and anticholinergic agents** for **emergency management** in adults with **asthma**. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD001284. Overall, combination inhaled therapy with SAAC and SABA reduced hospitalisation and improved pulmonary function in adults presenting to the ED with acute asthma. In particular, combination inhaled therapy was more effective in preventing hospitalisation in adults with severe asthma exacerbations who are at increased risk of hospitalisation, compared to those with mild-moderateexacerbations, who were at a lower risk to be hospitalised. A single dose of combination therapy and multiple doses both showed reductions in the risk of hospitalisation among adults with acute asthma. However, adults receiving combination therapy were more likely to experience adverse events, such as tremor, agitation, and palpitations, compared to patients receiving SABA alone.

Kirkland SW, Cross E, Campbell S, et al. **Intramuscular versus oral corticosteroids to reduce relapses following discharge from the emergency department for acute asthma**. Cochrane Database Syst Rev. 2018 Jun 2;6:CD012629. There is insufficient evidence to identify whether IM corticosteroids are more effective in reducing relapse compared to oral corticosteroids among children or adults discharged from an ED or equivalent acute care setting for acute asthma. While we found no statistical differences, patients receiving IM corticosteroids reported fewer adverse events. Additional studies comparing the effectiveness of IM versus oral corticosteroids could provide further evidence clarity. Furthermore, there is a need for studies comparing different IM corticosteroids (e.g. IM dexamethasone versus IM methylprednisone) and different oral corticosteroids (e.g. oral dexamethasone versus oral prednisone), with consideration for dosing and pharmacokinetic properties, to better identify the optimal IM or oral corticosteroid regimens to improve patient outcomes. Other factors, such as patient preference and potential issues with adherence, may dictate practitioner prescribing.

Kit BK et al. Trends in **Preventive Asthma Medication Use** Among **Children and Adolescents**, 1988-2008. Pediatrics. 2011 Dec 5.

Klijn P, van Keimpema A, Legemaat M, et al. **Nonlinear exercise training** in advanced chronic obstructive pulmonary disease is superior to traditional exercise training. A randomized trial. Am J Respir Crit Care Med. 2013 Jul 15;188(2):193-200.

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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Kopsaftis Z, Yap HS, Tin KS, et al. **Pharmacological and surgical interventions** for the treatment of gastro-oesophageal reflux in adults and children with asthma. Cochrane Database Syst Rev. 2021 May 17;5(5):CD001496.

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Kouri A, Boulet LP, Kaplan A, Gupta S. An evidence-based, point-of-care tool to guide completion of asthma **action plans** in practice. Eur Respir J. 2017 May 1;49(5).

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Kozer E, Lotem Z, Elgarushe M, et al. RCT of **Montelukast** as Prophylaxis for Upper Respiratory Tract Infections in Children. Pediatrics. 2012 Jan 4. (12 week 4mg oral not effective)

Kravitz J, Dominici P, Ufberg J et al. **Two Days** of Dexamethasone Versus 5 Days of **Prednisone** in the Treatment of Acute Asthma: A Randomized Controlled Trial. Ann Emerg Med. 2011Feb17.

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.

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Kruis AL, Smidt N, Assendelft WJ, et al. Cochrane corner: is **integrated disease management** for patients with **COPD** effective?. Thorax. 2014 Jan 14.

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Lazarus SC. Clinical practice. **Emergency treatment of asthma**. N Engl J Med. 2010 Aug 19;363(8):755-64.
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Nair P, Milan SJ, Rowe BH. Addition of **intravenous aminophylline** to inhaled beta(2)-agonists in adults with acute asthma. Cochrane Database Syst Rev. 2012 Dec 12;12:CD002742. doi: 10.1002/14651858.CD002742.pub2. The use of intravenous aminophylline did not result in significant additional bronchodilation compared to standard care with inhaled beta(2)-agonists in patients experiencing an asthma exacerbation in the ED setting, or in a significant reduction in the risk of hospital admission.

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Najafzadeh M, Marra CA, Sadatsafavi M, Aaron SD, Sullivan SD, Vandemheen KL, Jones PW, Fitzgerald JM. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. Thorax. 2008 Nov;63(11):962-7. Epub 2008 Jul 11. TFS had significantly better quality of life and fewer hospitalisations than patients treated with TP but these improvements in health outcomes were associated with increased costs. Neither TFS nor TS are economically attractive alternatives compared with monotherapy with T. (T=tiotropium)

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

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.

Nannini LJ, Poole P, Milan SJ, et al. **Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo** for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013 Nov 10;11:CD003794. Combined inhaler therapy led to around a quarter fewer COPD exacerbations than were seen with placebo. A significant reduction in all-cause mortality was noted, but this outcome was dominated by one trial (TORCH), emphasising the need for further trials of longer duration. Increased risk of pneumonia is a concern; however, this did not translate into increased exacerbations, hospitalisations or deaths.

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Navanandan N, Federico M, Mistry RD. **Positive Expiratory Pressure** for the Treatment of Acute Asthma Exacerbations: A Randomized Controlled Trial. J Pediatr. 2017 Mar 8.

Newman NC, Ryan PH, Huang B, et al. **Traffic-Related Air Pollution** and **Asthma** Hospital Readmission in Children: A Longitudinal Cohort Study. J Pediatr. 2014 Mar 25.

Ni CM, Greenstone I, Lasserson TJ, et al. **Addition of inhaled long-acting beta2-agonists to inhaled steroids** as first line therapy for persistent asthma in steroid-naive adults and children. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD005307. In steroid-naive patients with mild to moderate airway obstruction, the combination of ICS and LABA does not significantly reduce the risk of patients with exacerbations requiring rescue oral corticosteroids over that achieved with a similar dose of ICS alone. However, it significantly improves lung function, reduces symptoms and marginally decreases rescue ss2-agonist use. Initiation of a higher dose of ICS is more effective at reducing the risk of exacerbations requiring rescue systemic corticosteroids, and of withdrawals, than combination therapy. Although children appeared to respond similarly to adults, no firm conclusions can be drawn regarding combination therapy in steroid-naive children, given the small number of children contributing data.

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Ni CM, Lasserson TJ, Greenstone I, et al. Addition of **long-acting beta-agonists** to inhaled corticosteroids for chronic asthma in **children**. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD007949. In children with persistent asthma, the addition of LABA to ICS was not associated with a significant reduction in the rate of exacerbations requiring systemic steroids, but was superior for improving lung function compared to the same dose of ICS. Similarly, compared to a double dose ICS, the combination of LABA and ICS did not significantly increase the risk of exacerbations requiring oral steroids, but was associated with a significantly greater improvement in PEF and growth. The possibility of an increased risk of rescue oral steroids and hospital admission with LABA therapy needs to be further examined.

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NICE Oct/10 Guidance: **Omalizumab** for the treatment of severe persistent allergic asthma in children aged 6-11. http://www.nice.org.uk/nicemedia/live/13256/51345/51345.pdf

NICE: 2010 CG101 **Chronic obstructive pulmonary disease** (update): full guideline. London: National Institute for Health and Clinical Excellence, 2010. (http://guidance.nice.org.uk/CG101/Guidance .)

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NICE: National Institute for Health and Care Excellence (NICE). **Asthma: diagnosis, monitoring and chronic asthma management** https://www.nice.org.uk/Guidance/NG80 **2017**

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

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Peytremann-Bridevaux I, Arditi C, Gex G, Bridevaux PO, Burnand B. **Chronic disease management programmes** for adults with **asthma**. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD007988. DOI: 10.1002/14651858.CD007988.pub2. There is moderate to low quality evidence that chronic disease management programmes for adults with asthma can improve asthmaspecific quality of life, asthma severity, and lung function tests. Overall, these results provide encouraging evidence of the potential effectiveness of these programmes in adults with asthma when compared with usual care

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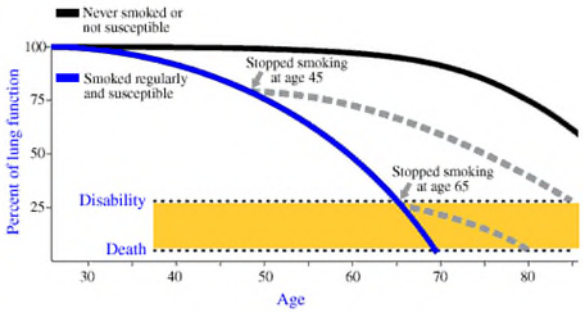

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Canadian Network For Asthma Care (CNAC) http://www.cnac.net?english/clinics.html

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

COPD

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COPD Online Extras

Increased risk of pneumonia when using an ICS in a COPD patient				
Trial	**FEV_1**	**Comparators**	**Pneumonia rates**	**↑ risk per year**
TORCH [16]	44%	LABA	13.3% over 3 years	2% per year
		LABA/**ICS**	**19.6%** over 3 years	
FLAME [45]	44%	LABA/LAMA	3.2% over 1 year	1.6% per year
		LABA/**ICS**	**4.8%** over 1 year	
IMPACT [46]	45%	LABA/LAMA	2.6% over 1 year	1.8% per year
		LABA/LAMA/**ICS**	**4.4%** over 1 year	

Methodology issues in **IMPACT** and **ETHOS** trials, which studied adding ICS therapy in COPD.

1. Enrollment of asthmatics. **IMPACT** did not exclude asthmatics. **ETHOS** excluded patients with a current diagnosis of asthma, but not with a past history of asthma. Around 20-30% of patients in each trial had a reversable FEV1 (i.e. a hallmark of asthma). Of course, an ICS would be expected to be of great benefit to patients with asthma.

2. Abrupt withdrawal of ICS upon enrollment. Over 70% of patients in **IMPACT** and over 80% of patients in **ETHOS** were on an ICS prior to the start of the trial. Most patients in the LAMA/LABA arms of these trials would thus have had their ICS abruptly stopped once the trial began. This appeared to artificially increase exacerbation rates:

ETHOS subgroup	**exacerbations per year**
On ICS throughout the trial	1.08
Not on an ICS before or during the trial	1.11
On an ICS before trial, and ICS stopped suddenly when trial began	1.51

In both trials, the Kaplan-Meier curves separated immediately (within 4 weeks of trial start). This is suspicious, and in line with a sudden withdrawal of ICS therapy leading to extra exacerbations. At the one-year mark, the Kaplan Meier curves were trending closer together, and if the trial had continued longer, ICS therapy might well have shown no benefit.

Search Terms

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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.

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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.

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ASTHMA & COPD: Inhalation Devices Chart

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Cystic Fibrosis Chart

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ATROVENT	200
Aztreonam	200
BRICANYL	200
CAYSTON	200
Colistimethate	200
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COTAZYM	200
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DEY-PAK	200
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TOBACCO USE DISORDER / SMOKING CESSATION Online Notes

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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.

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.

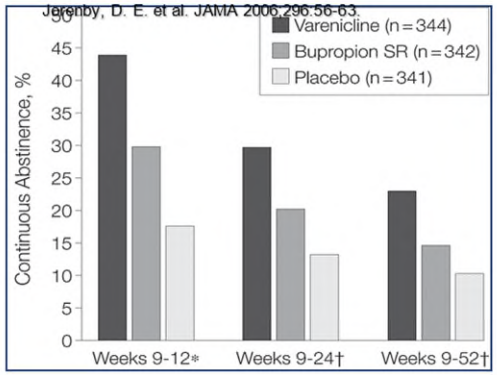
CHAMPIX / Varenicline – for Smoking Cessation

- **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)

Jorenby, D. E. et al. JAMA 2006;296:56-63.



- 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

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

AVENTYL	201
Bupropion	**201**
CESTEMENOL	201
CHAMPIX	201
CHANTIX	201
Cigarette	201
CRAVV	201
Cytisine	201
E-cigarette	201
ENDS	201
HABITROL	201
JUUL	201
NICODERM	201
NICORETTE	201
Nicotine	201
Nortriptyline	201
RESOLVE	201
Smoking	**201**

THRIVE	201
Tobacco	201
Varenicline	201
WELLBUTRIN	201
ZYBAN	**201**

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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.
FDA Dec/16 review of a large clinical trial that FDA required the drug companies to conduct, FDA determined the **risk of serious side effects on mood, behavior, or thinking** with the stop-smoking medicines **Chantix** (varenicline) and Zyban (bupropion) is lower than previously suspected. The risk of these mental health side effects is still present, especially in those currently being treated for mental illnesses such as depression, anxiety disorders, or schizophrenia, or who have been treated for mental illnesses in the past. As a result of the large clinical trial review, **FDA is removing the Boxed Warning**, FDA's most prominent warning, for serious mental health side effects from the Chantix drug label. The language describing the serious mental health side effects seen in patients quitting smoking will also be removed from the Boxed Warning in the **Zyban** label. FDA is also updating the existing warning section in both labels that describes the side effects on mood, behavior, or thinking to include the results from the clinical trial.
FDA Apr/19: E-cigarette: Safety Communication - Related to **Seizures Reported Following E-cigarette Use**, Particularly in Youth and Young Adults.
FDA May/19 has become aware that some people who use e-cigarettes have experienced seizures, with most reports involving youth or young adult users.
FDA Jun/19: Drip More, LP (Drip More) is voluntarily recalling four lots of Candy King – Worms 3mg/100mL that were produced by a contract manufacturer. The product has been found to contain a higher concentration of nicotine than the label indicates.
FDA Sep/19: E-Cigarette Products: Safety Communication - Due to the Incidents of **Severe Respiratory Disease Associated with Use of an E-Cigarette Product**.
FDA Oct/19 is strengthening its warning to consumers to stop using vaping products containing THC amid more than 1,000 reports of lung injuries—including some resulting in deaths—following the use of vaping products. FDA on Friday urged consumers to stop using vaping products that contain tetrahydrocannabinol (THC) or any vaping product obtained off the street, from friends, or otherwise illicitly. The recommendation came a day after the CDC reported 1080 cases of lung injury tied to vaping, with most involving THC. In its warning, the FDA also advised the following: Don't add THC, other oils, or any other substances to vaping products. Children and pregnant women shouldn't vape. Adults who use e-cigarettes as a replacement for traditional cigarettes should not return to traditional cigarettes. Those who vape should be on alert for symptoms like coughing, shortness of breath, and chest pain and should seek medical attention if they're concerned about their health. The agency also noted that it hasn't approved any vaping product for "therapeutic uses."
FDA Oct/19: is strengthening its warning to consumers to **stop using vaping products containing THC** amid more than 1,000 reports of lung injuries—including some resulting in deaths—following the use of vaping products.
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Health Canada July/07 Unauthorized Smoking Cessation Product **Resolve** May Pose Health Risk - Consumer Information. The product contains an unacceptable amount of an ingredient labelled as "CESTEMENOL-350." Consuming excessive amounts of this ingredient might result in damage to the kidney, liver or red blood cells.
Health Canada June/08 Pfizer Canada in collaboration with Health Canada would like to notify healthcare professionals of important safety information regarding **CHAMPIX**, and post-marketing reports of serious **neuropsychiatric adverse events**, including depressed mood, agitation, hostility, changes in behaviour, suicidal ideation and suicide, as well as worsening of pre-existing psychiatric illness (previously diagnosed or not). Since introduction of CHAMPIX in Canada, in April 2007 through April 30, 2008, a total of **226 Canadian cases** of neuropsychiatric adverse events have been reported. For the same time period, there have been **708 534 prescriptions filled** for CHAMPIX in Canada1. All patients attempting to quit smoking with CHAMPIX, their families & caregivers should be alerted about the need to monitor for symptoms of neuropsychiatric adverse events. Patients should be instructed to stop taking CHAMPIX and contact their healthcare provider immediately if they have or if their families or caregivers observe depressed mood, agitation, hostility or changes in behavior, that are not typical for the patient, or if the patient has suicidal ideation or suicidal behavior. Patients with concomitant psychiatric conditions, even if well controlled, or with a history of psychiatric symptoms, should be diligently monitored.
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 (**bupropion** 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.
Health Canada Jun/2021Testing results received from Pfizer Canada ULC identified 5 lots of CHAMPIX (varenicline) with levels of a **nitrosamine impurity, N-nitrosovarenicline,** above the acceptable intake limit established by Health Canada.
As a result, Health Canada requested that Pfizer Canada ULC recall the 5 impacted lots.
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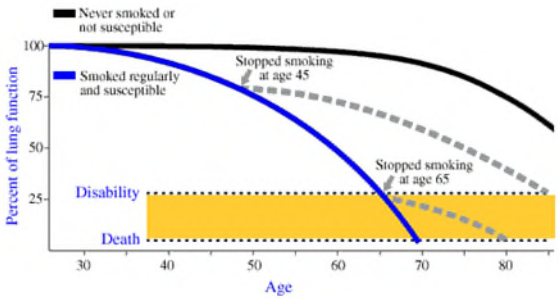

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Academic Detailing:

Canada

- BC CDUP: http://www.cdup.org/
- Dalhousie: http://cme.medicine.dal.ca/ADS.htm
- Saskatchewan: www.rxfiles.ca
- Ontario: https://cep.health/academic-detailing/
- Alberta: https://acfp.ca/advocacy/partnerships-collaborations/peer/

Non-Canadian

- Academic Detailing – National Resource Centre for Academic Detailing (USA): http://www.narcad.org/
- Pennsylvania (RxFacts.org): http://www.rxfacts.org/detailing.php
- Vermont Academic Detailing Program: https://www.med.uvm.edu/ahec/vermontacademicdetailing
- Australia – National Prescribing Service (NPS): https://www.nps.org.au/

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http://www.cpjournal.ca/doi/abs/10.3821/145.3.cpj142

OTC (OVER-THE-COUNTER) PRODUCTS: Online Extras

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Below are simplified charts for Acne, Fungal Infections, Dyspepsia, Irritable Bowel Syndrome, Constipation, Probiotics, Pain Relief, Warts, and Head Lice.
Clicking the above links will bring you to expanded versions of the charts for these disease states.

COMPLAINT & TREATMENT NOTES	SELECTED AGENTS	Usual Adult Dose; Daily MAX dose Pediatric Dose	$	Adverse Events (AE), Contraindications (CI), Drug Interactions (DI), Comments
ACNE 36-42 • Cause: multifactorial → follicular hyperkeratinization, *C. acnes* bacteria, sebum production, inflammation • Assess for drug-induced acne (anabolic steroids, carbamazepine, corticosteroids, lithium, phenytoin, etc.) • Non-Pharmacological Tx ○ Washing face ≤BID with mild soap/soapless cleanser (aseptic cleaners are not effective in ↓*C. acne*); avoid scrubbing ○ Eat a balanced diet avoiding "triggers" ?Avoid high glycemic or ↑ dairy ○ Use oil-free cosmetics and moisturizers ○ Avoid picking & squeezing lesions to prevent scarring • OTC Tx: for mild-mod acne (comedonal or papulopustular) **Benzyl Peroxide** (**BP**) for comedonal & **papulopustular acne**; **salicylic acid** (**SA**) offers no advantage over BP but useful for comedonal acne • Consider early & possible combination therapy to ↓scarring/dyspigmentation risk	**Benzoyl Peroxide** BENZAGEL PL 2.5, 5% OTC, 10% Rx in lotion, gel, crm rarely	Refer to each product label for exact instructions **General:** do not spot treat; apply to entire affected area gently clean face prior to application **BP**: due to AE, best to start at low concentration and build tolerance slowly - e.g. If sensitive skin **apply HS** x 15mins then wash off on day 1, then double the application time on subsequent days until pt can tolerate 4hr, then leave on overnight (30 mins on day 2, 1hr on day 3 etc.) If skin not too sensitive, may be able to use 1hr x 2 nights, then 2hrs x 2 nights, until increased to overnight within a week.	CLEAN & CLEAR 11/28g	AE: skin irritation, redness, BP can bleach hair & clothing ○ All products: start at low concentration and titrate up **BP**: most effective OTC agent, esp. inflammatory acne ○ **Antibacterial**, mild comedolytic & ↓sebum production ○ Does not promote antimicrobial resistance with long-term use ○ Minimal efficacy differences between concentrations; **2.5%=5%** <10% for AE; gels>creams> lotion in potency ○ Start with low concentration & water based formulation (i.e. 2.5% lotion); then change vehicle, 5% or to BID if needed ○ Often used in **combo** with topical retinoids and po antibiotics to ↓antibacterial resistance and ↑efficacy **SA**: comedeolytic, mild anti-inflammatory & antibacterial ○ Option for pts intolerant or unable to access retinoids/BP ○ Concentration <2% may ↑keratinization • Medicated soaps, washes and foams usually have uncertain benefit due to limited contact time • All tx may require 2-3 months for improvement; sx often worsen before they get better
	Salicylic Acid PL 0.5 to 2% usually ©		6-13	
	Glycolic Acid **Resorcinol** ?Efficacy **Sulfur** © PL		various	
	Consider **Rx preps** if no improvement after 6-8wks at BP 5% lotion/crm. See also: Acne Treatment pg. 31-32 *Topical Retinoids* (**Adapalene**, **Tretinoin**, **Tazarotene**) for mild-mod comedonal and papulopustular acne *Combo Tx* (**BP+Retinoids**, **BP+Abx**, **Retinoids+Abx**) for mild-mod comedonal and papulopustular acne *Oral Contraceptives* (**TRI-CYCLEN**, **ALESSE**, **DIANE-35**, **YASMIN**, **YAZ**): for extensive mild-mod papulopustular acne *Oral Antibiotics* (**tetracyclines**, **erythromycin**, **trimethoprim**): for extensive mild-mod papulopustular acne, severe acne (+BP ± Retinoids) **Isotretinoin** ACCUTANE for severe acne on SPDP, ▼ PL			
FUNGAL INFECTIONS 43,44 • Keep skin clean and dry (dry skin with hair dryer, use non-medicated, non-corn starch powders) **Tinea Pedis (Athlete's Foot)**: interdigital, hyperkeratotic or vesiculobullous eruptions on feet; may be painful or pruritic **Tinea Corporis (Ringworm)**: red, itchy, scaling patch/plaque with central clearing on trunk/extremeties **Tinea Cruris (Jock Itch)**: Red, itchy rash symmetrical on upper inner thigh and groin; penis/scrotum usually spared • Tx Tinea: Topical azole, tolnaftate, (terbinafine, ciclopirox) Rx ; oral flu- (itra-conazole, terbinafine) Rx if topical fails. **Nystatin ineffective**! ○ Tolfnate is less effective and leads to more recurrences than azoles ○ Terbinafine may be slightly more effective than azoles and have shorter duration of tx 45 **Vaginal Candidiasis** 46 **Tolnaftate not effective**! • Sx: vaginal irritation, itchiness, redness dysuria, dyspareunia, white curd-like vaginal discharge • Tx: Topical azole, nystatin, (terbinafine, ciclopirox) Rx; oral azole if topical tx fails, widespread region, or pt immunocompromised. ○ No one agent is superior to another for topical antifungal tx ○ Oral=topical in efficacy; single 150mg fluconazole as alternative tx	TOPICAL **Clotrimazole** 1% crm on SPDP, ▼ OTC PL CANESTEN PL **Miconazole** 2% crm on SPDP, ▼ MICATIN	Apply to affected area BID x2 Corporis, Cruris - 4 Pedis weeks, continue treating 1-2wks after sx disappears, to max of 4 wks	10/30g, g 11/30g	• Topical agents: AE: local irritation, redness, burning, itching, stinging Tinea Infections: • Apply topicals on the lesion and 2-5cm outside of it • Exact duration of tx unclear (except terbinafine - apply daily x 1wk); usually recommended to apply x 2wks or until 1wk after skin clears • Foul odour may indicate secondary bacterial infection • Recurring tinea pedis/cruris may be a sign of toenail infection requiring Rx systemic therapy • Not contagious after 24hr of therapy • **Pregnancy**: Clotrim- &micon-azole are drugs of choice Vaginal Candidiasis: • Self-diagnosis is common and often inaccurate 47 • 1-3 day regimens as effective as 6-7 days and improves adherence • Recurrent/resistant infection may need 3-4wks tx; fluconazole 150mg po weekly effective • **Pregnancy**: Sx may be severe and prolonged ○ Topical azoles recommended over nystatin or oral azole47 ○ Tx for 7 days; re-treatment may be needed ○ Avoid oral fluconazole (1st trimester exposures may lead to birth defects and spontaneous abortions)
	Tolnaftate 1% crm x ▼ TINACTIN PL	Apply to affected area BID x2 Corporis - 4 Pedis, Cruris weeks **Not effective for candida infections**	13/15g	
	VAGINAL **Clotrimazole** CANESTEN OTC PL (1,2%) on SPDP, ▼, 10% crm x ⊗; PL (200mg, 500mg tab) x ⊗ **Miconazole** MONISTAT (2% crm, 400mg) on SPDP, ▼, (4% crm; 100mg, 1200mg) x ⊗	Insert 1 applicatorful into the vagina daily at HS x 1d 10% crm, x3d 2% crm or x 6d 1% crm Insert 1 tab into the vagina daily HS x 1 500mg or x3 200mg days Insert 1 applicatorful into the vagina daily HS x 3 4% or x7 2% days Insert 1 tab into the vagina daily HS x 3 400mg or x 7 days 100mg Creams: apply to external perineum & vulvar area BID $5-8/15g	~19 or ~15, g 16-18	
	Combo Products: combination of (vaginal tab + external cream) or (vaginal cream+external cream) CANESTEN: CANESTEN COMBI 1 DAY vaginal/external cream; vaginal tab/external crm on SPDP, ▼, COMBI 3 DAY tab/crm on SPDP, ▼ MONISTAT: MONISTAT 1 COMBI PACK tab/crm x ⊗, 3 DUAL-PAK tab/crm on SPDP, ▼, 7 DUAL-PAK tab/crm on SPDP, ▼			
	Nystatin on SPDP, ▼ 100,000 unit/g, 250,000 unit/g crm PL	Insert 1 applicatorful into the vagina daily (q12h if severe) x 2wks **Not effective for dermatophyte infections**	21/75g	
	Fluconazole on SPDP, ▼ CANESORAL P1,2 PL	1 cap (150mg) po as a single dose	13/1tab, g	
	Rx preps: See also: Antifungals pg. 81-83 PL **Terbinafine** on SPDP, ▼ LAMISIL 1% crm,1% topical spray ⊗,250mg tab. Apply to affected area daily x 1-2wks **Ciclopirox** LOPROX 1% crm on SPDP, ▼, 1% lotion ▼. Apply to affected area BID x 2-4wks			

COMPLAINT & TREATMENT NOTES	SELECTED AGENTS Generic/TRADE	Usual Adult Dose; Daily MAX dose / Pediatric Dose	$	Adverse Events (AE), Contraindications (CI), Drug Interactions (DI), Comments
DYSPEPSIA/GERD **Must consult physician if sxs persist >2wks** • Predominant Sx: **epigastric pain** (dyspepsia) or **acid regurgitation /heartburn** (GERD). Other sxs: fullness, nausea, vomiting. • Diet/Lifestyle ? unlikely to help: weight loss, raise head of bed, avoid precipitating and aggravating factors (e.g smoking, alcohol)[21] • Tx **heartburn**: **Alginate**, **Antacids**, **H2RAs**, **PPIs** ○ Alginate/Antacids, H2RAs for mild, infrequent sx; H2RAs more effective in ↓frequency/severity of heartburn vs. antacids [21] PPIs 1st line for mod sx (more effective & faster sx relief vs. H2RAs) • Tx **epigastric pain**: OTC may provide relief for infrequent or unpredictable episodes of dyspepsia; [20] little evidence available ○ <60yrs: H.Pylori testing + tx if positive results; if negative, tx with PPI, then prokinetic/TCA if unresolved [ACG/CAG'17] • Recommendations for endoscopy (controversial): ○ >60yrs with dyspepsia; refrain in <60yrs even if alarm sxs [ACG/CAG'17] ○ >50yrs with new-onset dyspepsia, and all pts with alarm features[CMAJ'00]	*Antacids/Protectants* OTC **Sodium Alginate** GAVISCON **Aluminum Hydroxide** ALUGEL **Magnesium-Aluminum Hydroxide** DIOVOL **Magnesium Hydroxide**▼ Milk of Magnesia (MOM) **Calcium Carbonate**▼ TUMS	Onset: 5min; duration 30-60 mins PL Refer to dosing instructions on each product label; Usually taken 1hr after meals & HS	8/10tab 7/425mL 7/350mL 8/350mL 4/72tab	• **Antacids** available in both tabs and liquid form; liqu most efficacious • Mg^{++} & Al^{+++} antacid combo: constipating effects of Al^{+++} counterbalanced by laxative effects of Mg^{++} • **Antacids** DI: interfere with the absorption of some drugs (bisphosphonates, digoxin, iron, tetracycline & quinolones, levothyroxine); space 2-4hr apart • Avoid sodium bicarbonate due to high Na^+ content • Many ⓒ: e.g. PEPCID Complete (famotidine/calcium carbonate/ magnesium hydroxide) • **H2RA**: tachyphylaxis seen after 2-6weeks initiation • Others: bismuth subsalicylate PEPTO BISMOL 30mL or 2 tabs q30-60min prn; max 8 doses/day- see also in diarrhea • Pregnancy: initial tx with alginate/antacid, followed by H2RAs (ranitidine, cimetidine[Rx]), then PPIs (ome-, lanso[Rx]-,panto[Rx]- prazole)
	H2-Receptor Antagonists OTC **Famotidine** PEPCID AC 10, 20mg PL **Ranitidine** ZANTAC 75 PL 75, 150mg on SPDP, ▼ tab	Onset: rapid; duration 4-10 hours ≥12yrs: 1 tab (10mg) po PRN x 2wks; 40mg/d ≥16yrs: 1 tab (75mg or 150mg) po PRN x 2wks; 2 tabs/d	12/30tab,g 10/30tab,g	
	Proton Pump Inhibitors OTC **Omeprazole** 20mg cap on SPDP,▼ PL **Esomeprazole** 20mg cap ☎, ⊗	Onset: slow [2-3d to reach steady state inhibition]; 48 hours [246] ≥18yrs: 1 cap (20mg) po daily in am x 2wks; 1cap/d ≥18yrs: 1 cap (20mg) po daily in am x 2wks; 1cap/d	11/14tab 14/14tab	
	See also: H.pylori chart pg. 71, GERD & Peptic Ulcer Disease chart pg. 70			
IRRITABLE BOWEL SYNDROME: characterized by disordered intestinal motility & alternating bouts of constipation & diarrhea. Tx: lifestyle changes (e.g. avoiding food triggers, adequate diet, fibre, fluids, exercise); symptomatic tx (loperamide for diarrhea, fiber for constipation, antispasmodic if indicated); tx underlying psychosocial co-morbidity. Rx products such as antidepressants[ELAVIL], antispasmodics[BUSCOPAN] may help. See: IBS chart pg. 72.				
CONSTIPATION [22-25] See also: laxatives pg. 61-64 • Cause: drug-induced (e.g. anticholinergics, opioids, antacids with aluminum, calcium or iron, high dose diuretics, clonidine, CCBs esp verapamil, TCAs), functional (no drug or anatomic cause), fecal impaction. Treat underlying causes where possible • Ensure adequate dietary fibre intake (25-30g/day) with fluid ○ ↑ intake by ~5g/day from fruits & vegetables or ○ Begin with 1-2tbsp/d wheat bran and ↑ up to 2-4 tbsp/d • Adequate fluid intake & regular exercise • Tx: **bulk-forming agents**, **osmotic agents**, **stimulants** ○ Psyllium has the most efficacy data ○ PEG is more effective than lactulose [26] ○ Docusate COLACE appears ineffective. [22]	*Bulk-Forming Agents* OTC PL **Psyllium**▼ METAMUCIL **Inulin** BENEFIBRE **Methylcellulose** CITRUCEL	Start low-AE: gas/bloating from bacteria degrading fibre 7g in 240mL liquid po daily–TID (6-12yrs: 3.5g up to TID) 1-2tsp po up to BID (6-12yrs: half the adult dose) 1 tbsp po daily – TID (6-12yrs: 2.5 tsp daily- TID)	22/662g 17/340g 13/850g	• AE: bloating, abdominal discomfort, flatulence common with most; stimulants & osmotics can cuase cramping, abdominal pain, and diarrhea • **Onset of Action**: bulk-forming agents over days; PEG, lactulose, sorbitol within 24-48hrs; stimulants and MOM within 6-12hrs and suppositories within 1hr • **Bulk-forming, lactulose, PEG**, (& docusate ?efficacy) OK for chronic use; stimulant and other osmotic for short-term occasional use (1-2days duration, 1/wk); except stimulants for opioid-induced constipation • **Stimulants** have overuse potential & chronic use may lead to electrolyte imbalance or dehydration in some • Pregnancy: fibre and bulk-forming initially → PEG, lactulose or short term MOM → then stimulant [short term]
	Osmotic Agents OTC **PEG 3350**▼ RESTORALAX, LAX-A-DAY PL **Lactulose**▼ 667mg/mL PL **Glycerin**▼ PL **Magnesium Hydroxide**▼ MOM PL **Phosphate**▼ FLEET PL	17g (1 capful) in 250mL fluid po daily (2-18y: 0.4-0.8g/kg/d) 15-30mL po daily-BID (6-12y: 10mL BID, 1-5y: 5mL BID) 1 suppository pr PRN 15-30mL po daily-BID (80-240mg/kg po daily) 120mL as rectal enema (2-12yrs: 60mL rectal enema)	15/238g,g 10/500mL,g 5/24sup,g 8/350mL 7/130mL	
	Stimulants OTC **Senna**▼ SENOKOT PL **Bisacodyl**▼ DULCOLAX PL	SENOKOT: 2-4 tabs po daily-BID (6-12yrs: 1-2 tabs daily-BID) DULCOLAX: 5-10mg po daily (6-12yrs: 5mg daily) If daily, take HS ≥12yrs: 1 suppository pr PRN daily	7/30tab,g 10/30tab,g	
	Docusate Sodium COLACE ?Efficacy PL	100-200mg/d po (2-12yrs: 50-150mg/d)	7/100tab,g	
DIARRHEA [27-30] • Cause: infections (**viral**, bacterial, parasite), food/water, IBS, IBD, drugs (antibiotics, acarbose, chemo tx, cholinergics, colchicine, digoxin, metformin, Mg++, misoprostol, orlistat, SSRIs); ? severe anxiety/stress • Antibiotic-Induced Diarrhea: usually self-limiting; ○ Live culture yoghurt [≥1 billion CFU/serving] or probiotics ○ If severe/prolonged, assess for *C. difficile* • Oral Rehydration Therapy (ORT) important; esp. for peds/elderly ○ (PEDIALYTE, GASTROLYTE, HYDRALYTE) ▼ available commercially; GATORADE okay for mild-mod diarrhea in adults ○ ½ strength diluted apple juice/fluids for infants ○ Home-made: ½ tsp salt + 6 tsp sugar in 1L water [WHO] • Avoid sorbitol, xylitol, and other food triggers (e.g. lactose) • Tx: OTC tx is for mild-mod cases only (i.e. no fever, <2 days sx) **Bismuth subsalicylate** PEPTO BISMOL, **Loperamide** IMODIUM ○ Loperamide is more effective & provides faster relief vs. bismuth [29]	**Bismuth Subsalicylate**▼ OTC PL PEPTO-BISMOL	≥12yrs:30mL(524mg) q30min or 60mL q1h PRN;240mL/d Prophylaxis for Travellers' Diarrhea ≥12yrs: 524mg QID	7/230mL	• CI: <2yrs - focus on ORT/ lifestyle/ tx underlying cause! • **Loperamide** AE: cramps, dizziness, constipation **Bismuth** AE: black tongue/stool; beware of salicylate overdose & Reye's sx • **Loperamide** DI: Pgp[esp. verapamil], 3A4, QT prolonging agents Avoid if dysenteric sx or high fever→ may retain pathogens Other Tx Options: • **Attapulgite** KAOPECTATE may ↓severity/duration in mild-mod diarrhea, but less effective than loperamide [31,32] • **Psyllium** useful for sx control- absorbs fluids, adds bulk • po **Zinc** supplementation recommended for children in developing countries (↓severity/ duration) [WHO, UNICEF] Traveller's Diarrhea tx: do not routinely give cholera & *E.coli* vaccine DUKORAL [CATMAT'15]; but an option for adults is PEPTO BISMOL. "Boil it, Cook it, Peel it, or Forget it!"
	Loperamide on SPDP, ▼ IMODIUM PL OTC	4mg stat, then 2mg after each loose bowel movement; 16mg/d (max dose for 8-12yrs: 6mg/d; 6-8y: 4mg/d)	6/6tab,g	
	Attapulgite KAOPECTATE OTC PL	>12yrs: 1200-1500mg stat and after each loose bowel movement; 8400mg/d (max 6-12y: 4200mg/d; 3-6: 2100mg/d)	7/180mL	
	Probiotics OTC • Probably effective for preventing **antibiotic-induced diarrhea** in children [33; NNT=9] and adults [34; NNT~12] • Not effective in ↓severity/duration of gastroenteritis in children[35, AFP'18(1b)] • Possibly effective for prevention of *C.difficile* associated diarrhea, ? Recurrent abdominal pain in children ***Lactobacillus rhamnosus* GG** CULTURELLE ***Saccharomyces boulardii*** FLORASTOR ***Lactobacillus platarium* 299v** TUZEN ***Lactobacillus acidophilus, casei, & rhamnosus*** BIO-K **8 different species** Visbiome, VSL #3[not in Canada]	AE: generally well tolerated CI: immunocompromised/critically ill Caution: if worsens or persists >3d [medical tx ~$30/30tabs] See Also: probiotics chart pg. 117-118		
PAIN RELIEF • For self-limiting conditions of short duration - e.g. low back pain, dental pain, headache • Non-pharmacological tx (massage, hot/cold therapy, resuming physical acticity, physiotherapy) are useful • See also: NSAIDs & Other Analgesics (pg. 129), Opiates (pg. 130), Migraine & Headache (pg. 159-160), Back Pain (pg. 143)	**Acetaminophen**▼ TYLENOL OTC PL	325-1000mg q4-6hr; 3.2-4g/d ≤12yrs: 10-15mg/kg q4-6hr; 75mg/kg/d	500mg 8/120tab,g 325mg 11/120tab,g	• OTC pain relievers come in many strenths, formulations and combination products • **Acetaminophen** is in many combo products - ensure total max is <4g/day to avoid accidental overdose • Max OTC **ibuprofen** dose (1200mg/d) provides analgesia but not anti-inflammatory effects (need >1600mg/d) • NSAIDs ↑risk of kidney injury, hypertension, GI ulcers • Chronic use in headaches (≥10days/mon) may cause medication overuse headache (rebound headache)
	Acetylsalicylic Acid▼ ASPIRIN OTC $P_{1,2}P_3L$	≥12yrs: 325 - 1000mg q4-6hr; 4g/d Avoid in kids ≤12yrs due to risk of Reye's Syndrome	325mg 6/100tab,g 500mg 7/50tab	
	Ibuprofen▼ ADVIL $P_{1,2}P_3L$	200-400mg q6-8hr; 1.2g/d max for OTC 6mon-12yrs: 5-10mg/kg q6-8h; ≤40mg/kg/d max OTC	200mg 7/50tab,g 400mg 12/72tab,g	
	Naproxen▼ ALEVE $P_{1,2}P_3L$	220mg q8-12hr; 440mg/d max for OTC Not indicated OTC for kids <12yrs	12/100tab,g	

COMPLAINT & TREATMENT NOTES	SELECTED AGENTS	Usual Adult Dose; Daily MAX dose Pediatric Dose	$	Adverse Events (AE), Contraindications (CI), Drug Interactions (DI), Comments
PLANTAR WARTS [57-61]: Warts (benign skin proliferation caused by HPV) on the soles of the feet; hard, flat ± black pinpoint • 20-30% spontaneously resolve within 6 mons & 65% within 2yrs; but removal often desired due to stigma, pain, or to ↓spread • Avoid walking barefoot (e.g. in pools), avoid picking or scratching • Tx: **Salicylic Acid** (SA) & Cryotherapy as first line; other tx for refractory warts. See also pg 34. ○ SA has most evidence for efficacy;[~73% cure rate, 58] Cryotherapy may be as effective as SA[50-70% cure rate] ○ SA+cryotherapy is more effective than SA alone [RR=1.24, 60] ○ Liquid nitrogen is likely more effective vs. DMEP (lower temp achieved), but painful	For all: Wash and soak wart in warm water x 5 mins, then dry. May pare overlying keratoma & dead tissue (e.g. with a pumice stone) prior to application.			**Caution**: do not self-treat if diabetes, vascular disorder **AE** skin irritation, hypo/hyperpigmentation, pain and blistering for cryotherapy • **SA** requires long [3mons] and persistent tx for success • Weaker preps are for warts on thinner skin; may ↓AEs but requires more frequent application • Aggressive cryotherapy (longer application)[20-30sec] is more effective vs. gentle approach (shorter) • Rx: **CANTHARONE PLUS**, ?**ALDARA P**, ?**EFUDEX** • Many other options (lacking strong evidence) ○ Laser, ?Zinc; ?Duct tape (6 days on, 12hr off x 5-10 cycles)
	Salicylic Acid 12-40% Liquid, Gel, Patch **COMPOUND W**, **Dr.Scholl's OTC**	Refer to each product label for exact instructions **Liquid/Gel**: Apply daily-BID, up to 12 weeks **Patch**: Trim to match wart size; Apply q48h, up to 12wks	4-9/10mL	
	Cryotherapy **Dimethyl Ether/Propane (DMEP)** **WARTNER**, **Dr.Scholl's OTC** **Rx Liquid Nitrogen** PL	Refer to each product label for exact instructions **OTC:** Apply for ~20-40 sec depending on site, q2-3wks until wart clears; max 6 treatments (3 months) **Rx:** Applied in physician's office	23, g or 33/12app	
	Combo Products: **SA+DMEP** **DR SCHOLL'S DUAL ACTION**, **COMPOUND W DUAL POWER** Start SA 24hr after cryotherapy and treat x 2wks		~33	
HEAD LICE [62-64] see also pg 33 • Sx: pruritis (may be delayed 4-6wks), excoriations on scalp, neck • Diagnosis is based on presence of **live** lice (important to confirm due to rising resistance). Nits are often present even after successful tx; viable ones are laid ¼ inches from the scalp. • Examine all contacts & tx if active infestation (**do not prophylax**), launder bedding & cetain clothing; & vaccum rooms (not crucial) • "No Nit Policy" is discouraged [Devore AAP'15]; children can go back to school after initial tx (avoid head-head contact) • Tx: Use isopropyl myristate/ST-cyclomethicone or dimethicone; if tx fails use Pediculicides (**Pyrethrin/Permethrin**) as 2nd line [124]	For all: do not sit in bath water as hair is being rinsed. **OTC**			• **CI** **pyrethrin**: allergy to ragweed or chrysanthemum plant (reaction with **permethrin** less likely) • Try to differentiate between reinfestation/tx failure and product adverse effects (itching, rash, irritation) • Cure rate [2 applications]: **permethrin** 96-100%, **pyrethrin** 94%, **dimethicone** 97%, **isopropyl myristate** 57-93% • Oral cotrimoxazole [Rx] and ivermectin [Rx] sometimes used for refractory infestations or if large body area affected • Wet combing is poorly effective (38% cure rate) and does not ↑efficacy of pediculicides • Household or natural products (e.g. mayonnaise, olive oil, tea tree oil, Vaseline) are unlikely to be effective
	Isopropyl Myristate/ Cyclomethicone on SPDP,▼ **RESULTZ** PL *Noninsecticidal; dissolves exoskeleton*	≥2yrs: Saturate product on **dry** hair/scalp and leave on x **10min**. Rinse & Repeat in **7d**.	20	
	Dimethicone▼ **NYDA** PL *Noninsecticidal; suffocates lice overnight; has ovicidal activity*	≥2yrs: Spray product on **dry** hair and massage until hair is completey wetted. Leave on x **8h**. Rinse&Rpt x **8-10d**. Reasonable to consider for possible prophylaxis in some.	26	
	Permethrin **KWELLADA-P**, **NIX** PL *Pediculicide* on SPDP,▼	≥2mon: **Wash hair** without conditioner. Saturate product on hair/scalp and leave on x **10min**. Rinse&Repeat in **7d**.	16-21	
	Pyrethrin/Piperonyl Butoxide **R&C SHAMPOO** PL *Pediculicide* on SPDP,▼	≥2mon: Saturate product on **dry** hair/scalp and leave on x**10min**. Rinse&Repeat in **7d** (↑efficacy from 45 to 94%)	16	

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RxFiles Over-The-Counter (OTC) Chart- References [Sept 2019 update]

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221**.** Health Canada Jan/18 is advising Canadians that one bottle of children's "**Flintstones Plus Iron**" multivitamins (NPN 02247995) was returned to a pharmacy containing unidentified capsules instead of the proper chewable tablets, which are multi-coloured tablets shaped like Flintstones characters.
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236.

💻 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; Kayexalate)
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:

↑ 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, smoking **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.
Canadian Medical Association Journal 2007;177(4):369-71

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Herbal Drug Interactions: Online Extras

Useful Herbal Websites

www.fda.gov/food/dietarysupplements/default.htm
www.quackwatch.com
www.ncahf.org
www.herbmed.org
www.consumerlab.com
www.naturaldatabase.com
www.mskcc.org/aboutherbs
www.hc-sc.gc.ca/dhp-mps/prodnatur/index-eng.php
www.herbs.orgmedlineplus.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

Herbals with Frequent Allergic Reactions American Journal of Medicine, Feb 1998

Agnus, Castus, Angelica, Aniseed, Apricot, Arnica, Artichoke, Asafoetida, Boneset, Cassia, Celery, Cinnamon, Cowslip, Dandelion, Elecampane, Euphobia, Feverfew, Fucus, Gravel Root, Gauicum, Holy Thistle, Hops, Hydrangea, Juniper, Lady's Slipper, Meadowsweet, Motherwort, Parsley, Pilewort, Plantain, Pulsatilla, Rosemary, Royal Jelly, Tansy, Wild Carrot & Yarrow.

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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.
Australian Therapeutic Goos Administration Oct/15 : **ActiveSlim slimming capsules** contains undeclared sibutramine.
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Birks J, Grimley EV, Van Dongen M. **Ginkgo bilo**ba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2002;(4):CD003120. CONCLUSIONS: Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and we cannot exclude publication bias. Overall there is promising evidence of improvement in cognition and function associated with Ginkgo. However, the three more modern trials show inconsistent results. Our view is that there is need for a large trial using modern methodology and permitting an intention-to-treat analysis to provide robust estimates of the size and mechanism of any treatment effects.
Birdee GS, Phillips RS, Davis RB, Gardiner P. Factors associated with **pediatric use of complementary and alternative medicine**. Pediatrics. 2010 Feb;125(2):249-56. Epub 2010 Jan 25.
Birks J, Grimley Evans J. **Ginkgo biloba** for cognitive impairment and dementia. Cochrane Database Syst Rev. **2009** Jan 21;(1):CD003120. Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and publication bias cannot be excluded. The evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.
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CameronM, Chrubasik S. **Topical herbal therapies for treating osteoarthritis**. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD010538. DOI: 10.1002/14651858.CD010538. Although the mechanism of action of the topical medicinal plant products provides a rationale basis for their use in the treatment of osteoarthritis, the quality and quantity of current research studies of effectiveness are insufficient. Arnica gel probably improves symptoms as effectively as a gel containing non-steroidal anti-inflammatory drug, but with no better (and possibly worse) adverse event profile. Comfrey extract gel probably improves pain, and Capsicum extract gel probably will not improve pain or function at the doses examined in this review.
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Clegg et al . National Institutes of Health (NIH) Glucosamine/Chondroitin Arthritis Intervention Trial (**GAIT**) Clegg DO, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006 Feb 23;354(8):795-808. CONCLUSIONS: Glucosamine and chondroitin sulfate alone or in combination did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee. Exploratory analyses suggest that the combination of glucosamine and chondroitin sulfate may be effective in the subgroup of patients with moderate-to-severe knee pain. (The 1,538-pts GAIT trial compared the effectiveness & safety of these supplements taken alone and in combination in patients with painful knee osteoarthritis (WOMAC Pain 125-400 mm) treated at 16 academic medical centers in the U.S. The response rate for all patients was 60.1% in a placebo group, 64% in a glucosamine hydrocholoride arm (500 mg TID); 65.4% in a chondroitin alone arm (400 mg TID); & 66.6% in a glucosamine-plus-chondroitin arm (500 mg/400mg TID) (p=0.09), according to a study results reported at the American College of Rheumatology meeting in San Diego Nov/05). http://nccam.nih.gov/news/19972000/121100/qa.htm (InfoPOEMs: Glucosamine HCl and chondroitin provides modest if any symptomatic benefit for patients with mild osteoarthritis of the knee. This study was well designed and avoided many of the design flaws of earlier studies. However, it had a high dropout rate (20%) and used a different glucosamine salt than most previous studies. In addition, post-hoc analysis suggests a large benefit in patients with moderate to severe pain. There were also consistent trends toward benefit for many secondary outcomes. (LOE = 1b)) Sawitzke AD, Shi H, Finco MF, Dunlop DD, Bingham CO 3rd, Harris CL, Singer NG, Bradley JD, Silver D, Jackson CG, Lane NE, Oddis CV, Wolfe F, Lisse J, Furst DE,Reda DJ, Moskowitz RW, Williams HJ, Clegg DO. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: A report from the glucosamine/chondroitin arthritis intervention trial. (GAIT) Arthritis Rheum. 2008 Sep 29;58(10):3183-3191. [Epub ahead of print] At 2 years, no treatment achieved a predefined threshold of clinically important difference in JSW loss as compared with placebo. However, knees with K/L grade 2 radiographic OA appeared to have the greatest potential for modification by these treatments.
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Cohen PA, Wen A, Gerona R. Prohibited **stimulants in dietary supplements** after enforcement action by the US Food and Drug Administration [online Oct 22, 2018]. JAMA Intern Med. doi:10.1001/jamainternmed.2018.4846 FDA Oct/18: Fat Burners Zone is voluntarily recalling 1 lot of Zero Xtreme, capsules to the consumer level. FDA analysis has found Zero Xtreme to be tainted with sibutramine.
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JAMA. 2008 Nov 19;300(19):2253-2262. (n=3,069 6.1yrs) In this study, G biloba at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI.

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De Silva V, El-Metwally A, Ernst E, et al. Evidence for the efficacy of complementary and alternative medicines in the management of **osteoarthritis**: a systematic review. Rheumatology (Oxford). 2011 May;50(5):911-20. The available data for most complementary and alternative medicine (CAM) in treating patients with degenerative joint disease is limited. Topical **capsaicin** and S-adenosyl methionine (**SAMe**) appear to be effective in treating pain, but even these data are limited and potentially subject to bias in favor of publishing positive results. (LOE = 1a-)

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

Deng H, Xu J. **Wendan decoction** (Traditional Chinese medicine) for schizophrenia. Cochrane Database Syst Rev. 2017 Jun 28;6:CD012217. Limited evidence suggests that WDD may have some positive short-term antipsychotic global effects compared to placebo or no treatment. However when WDD was compared with other antipsychotics there was no effect on global or mental state, but WDD was associated with fewer adverse effects. When WDD was combined with an antipsychotic, positive effects were found for global and mental state and the combination caused fewer adverse effects.

Devarbhavi H, Choudhury AK, Sharma MK, et al. **Drug-Induced Acute-on-Chronic Liver Failure in Asian Patients**. Am J Gastroenterol. 2019 Apr 22.

Dhesi Pavittarpaul; Ng Rita; Shehata Michael M.; Shah Prediman K.. Ventricular Tachycardia After Ingestion of **Ayurveda Herbal** Antidiarrheal Medication Containing **Aconitum**. Arch Intern Med. 2010;170(3):303-305.

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

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.

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

Draves AH, Walker SE. Analysis of the hypericin and pseudohypericin content of commercially available **St John's Wort** preparations. Can J Clin Pharmacol. 2003 Fall;10(3):114-8.

Drieling RL.; Gardner CD.; Ma Jun; et al. No Beneficial Effects of **Pine Bark Extract** 200mg daily on Cardiovascular Disease Risk Factors. Arch Intern Med. 2010;170(17):1541-1547. n=130, 12 wk.

Edelman ER, Butala NM, Avery LL, et al. Case 30-2020: A 54-Year-Old Man with Sudden Cardiac Arrest**- Licorice**. N Engl J Med. 2020 Sep 24;383(13):1263-1275

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

El Refaeey A, Selem A, Badawy A. Combined **coenzyme Q10** and clomiphene citrate for ovulation induction in clomiphene- citrate-resistant polycystic ovary syndrome. Reprod Biomed Online. 2014 Jul;29(1):119-24.

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).

Eldridge WB, Foster C, Wyble L. Neonatal Abstinence Syndrome Due to **Maternal Kratom Use**. Pediatrics. 2018 Nov 7.

Enioutina EY, Job KM, Sherwin CMT. Why we need to pay attention to **toxicity associated with herbal medicines**. Br J Clin Pharmacol. 2020 May 13. doi: 10.1111/bcp.14340

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

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

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

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

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

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

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

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

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

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

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

FDA Nov/08 Balanced Health Products, Inc. announced a recall of **STARCAPS** due to the presence of an undeclared drug ingredient, Bumetanide. Bumetanide is a diuretic indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease including nephrotic syndrome.

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

FDA Dec/08 alerted consumers not to purchase or consume more than **25 different products** marketed for weight loss because they contain undeclared, active pharmaceutical ingredients that may put consumers' health at risk. The undeclared active pharmaceutical ingredients in some of these products include sibutramine (a controlled substance), rimonabant (a drug not approved for marketing in the USA), phenytoin (an anti-seizure medication), and phenolphthalein (a solution used in chemical experiments and a suspected cancer causing agent). The weight loss products, some of which are marked as "dietary supplements," are promoted and sold on various web sites and in some retail stores. FDA advises consumers who use the products to stop taking them and consult their healthcare professional immediately as the health risks posed by these products can be serious (for example, high blood pressure, seizures, tachycardia, palpitations, heart attack or stroke). FDA also encourages consumers to seek guidance from healthcare professional before purchasing weight loss products. See the FDA News Release for a listing of the names of the 25 referenced products. Read the MedWatch 2008 safety summary, including links to the News Release and Questions and Answers, at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Weight

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

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

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

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

FDA May/18: laboratory analysis confirmed that Best Candy contains nortadalafil.

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 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 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 007**contains 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.
FDA Dec/16 laboratory analysis confirmed that **Triple Green Capsules, Rhino 9 Premium 3500, Rhino 8 Platinum 8000, Rhino 7K 9000 Male Performance Booster, Duramaxxx, Rhino 5 1500, Lang Yi Hao, Bl4ck 4K capsules, Big Penis Male Sexual Stimulant, Power Male Sexual Stimulant, 90° Jiushidu capsules, Black Mamba 2 Premium, Black 3K Plus Male Sexual Enhancement Capsules & African Viagra** contains sildenafil.
FDA Dec/16 laboratory analysis confirmed that **Queen Slimming Soft Gel** contains sibutramine.
FDA Jan/17: **ABX Weight Loss, Ultimate Body Tox** has undeclared sibutramine.
FDA Jan/17: **Accelerator Boost** has undeclared phenolphthalein.
FDA Jan/17: **Results & Zi Su Body Fat Health II** has undeclared sibutramine and phenolphthalein.
FDA Jan/17: **Skinny Bee Diet** has undeclared desmethylsibutramine, sibutramine, and phenolphthalein.
FDA Jan/17: **Supreme Slim 5.7** has undeclared phenolphthalein and sildenafil.
FDA Jan/17: **Ready Man!** Has undeclared sildenafil.
FDA Jan/17: **Side Head Regulator TT Tablet** has high levels of lead.
FDA Jan/17 is warning consumers not to purchase or use **PNC-27**, a product promoted and sold through http://PNC27.com, as a treatment or cure for cancer. An FDA laboratory discovered the bacteria Variovorax paradoxus in a PNC-27 solution sample for inhalation.
FDA Jan/17 announced that its laboratory analysis found inconsistent amounts of **belladonna, a toxic substance, in certain homeopathic teething tablets**, sometimes far exceeding the amount claimed on the label.
FDA Feb/17 laboratory analysis confirmed that **Goldreallas XXX, Goldreallas Original, Ginseng for Reinforcing Kidney, Old Chinese, & Shenjingpian** contains sildenafil.
FDA Feb/17 laboratory analysis confirmed that **Lean Extreme Max, Slimming Plus Advanced, Platinum Weight Solution – Fat Loss Metabolizer & X-treme Beauty Slim** contains sibutramine.
FDA Feb/17 Kingsway Trading Inc. is recalling its 1.06 oz (30g) bottles of "**Well Balance Xanthium & Siler Combo (Bi Yan Pian)"** Batch No. 130401 & Batch No. 150201 because they contain the presence of undeclared Ephedra Herba (ma huang), an FDA banned item.
FDA Mar/17 laboratory analysis confirmed that **Arouse-Plus** contains tadalafil.
FDA Mar/17 laboratory analysis confirmed that **Bazook Bullet** contains aminotadalafil.

FDA Mar/17 **A&H Focal Inc**. is voluntarily recalling all lots marketed as dietary supplements for male sexual enhancement from January 2014 to present. These products have been historically tested by the FDA and found to contain PDE-5 Inhibitors (i.e.sildenafil, tadalafil, vardenafil, etc.).

FDA Mar/17: Regeneca Worldwide, a division of VivaCeuticals, Inc. is conducting a nationwide recall of its entire line of herbal and dietary supplement products pursuant to a Consent Decree entered by the federal court for the Central District of California. This recall applies to all products manufactured and sold between June 1, 2011 and February 8, 2017. These products include, but are not limited to **RegeneSlim, RegenErect, RegeneArouse**, **RegeneBlend, RegeneBoost, RegeneBlast, and RegeneFit**.

FDA Mar/17 analyzed samples of La Bri's Body Health Atomic and found it to contain the undeclared ingredient sibutramine.

FDA Apr/17 Organic Herbal Supply Supplement Products: Recall - undeclared Drug Ingredients: **Including Uproar, Cummor, Zrect, LabidaMAX, Monkey Business, Xrect, Rectalis, Tornado, Zdaily, BigNHard, Enhancerol Natural Male Enhancement capsules-** found the products to contain Tadalafil.

FDA May/17 laboratory analysis confirmed that **Big N Hard** contains tadalafil.

FDA May/17 laboratory analysis confirmed that **Cummor & Monkey Business** contains N-desmethyl tadalafil.

FDA May/17 laboratory analysis confirmed that **Xrect** contains tadalafil and descarbonsildenafil.

FDA May/17 laboratory analysis confirmed that **Tornado** contains nortadalafil.

FDA May/17 laboratory analysis confirmed that **Z Daily** contains homosildenafil.

FDA May/17 Genetic Edge Compounds recalled all lot codes of **GEC Laxoplex dietary supplement** capsules distributed between February 2, 2015- May 2, 2017 to the retail level and consumer level. FDA analysis found GEC Laxoplex to be tainted with anabolic steroids and steroid like substances

FDA May/17: Dynamic Technical Formulations LLC. is voluntarily recalling all lots of **Tri-Ton**. This product was sold in 90 count bottles as a dietary supplement and includes all lot number and expiration dates of the product. FDA lab analysis of Tri-Ton was found to contain andarine and ostarine which are selective androgen receptor modulators (SARMs) that are considered unapproved drugs and anabolic steroid-like substances.

FDA May/17: MusclMasster, LLC is recalling all bottles of **Al-Er-G Capsules**. During a recent FDA inspection, it was discovered that this product contained Ephedra Herb, an FDA banned ingredient.

FDA May/17 Caverflo.com is voluntarily recalling all lots of **Caverflo Natural Herbal Coffee**, 25 grams to the consumer level. FDA laboratory analysis confirmed the presence of Sildenafil and Tadalafil.

FDA Jun/17: FDA posted warning letters to Flex Fitness/Big Dan's Fitness, AndroPharm, and Hardcore Formulations for illegally marketed products labeled to contain steroid and steroid-like substances and promoted to increase muscle mass and strength.

FDA Jun/17 laboratory analysis confirmed that **XXX Zone Platinum & Triple Premium Zen Gold 1300mg** contains sildenafil, tadalafil and dapoxetine.

FDA Jun/17 laboratory analysis confirmed that **Triple X 2000** contains tadalafil and dapoxetine.

FDA Jun/17 laboratory analysis confirmed that **Macho Man 3000, Monster X 1350, Royal Master, & Love Zen 3000** contains tadalafil.

FDA Jun/17 laboratory analysis confirmed that **Own the Knight 1750** contains tadalafil and dapoxetine.

FDA Jun/17 laboratory analysis confirmed that **Xzone Gold, Super Panther 7K & Triple Miracle Zen Plus 1200mg** contains sildenafil and tadalafil.

FDA Jun/17 laboratory analysis confirmed that **Man of Steel 2 & Man of Steel** contains sildenafil.

FDA Jul/17: Hardcore Formulations is voluntarily recalling all lots and expiration dates of **Ultra-Sten and D-Zine capsules** to the consumer level. These products are labeled to contain methylstenbolone (Ultra-Sten) and dymethazine (D-Zine), which are considered to be derivatives of anabolic steroids.

FDA Jul/17: Andropharm is voluntarily recalling all lots of **Sten Z and M1 Alpha capsules** to the consumer level because these products contain derivatives of anabolic steroids rendering them unapproved drugs for which safety and efficacy have not been established and therefore subject to recall.

FDA Jul/17 laboratory analysis confirmed that **Kingdom Honey for Her, Kingdom Honey for Him, & Royal Honey VIP** contains tadalafil.

FDA Jul/17 laboratory analysis confirmed that **Rhino 7 Platinum 5000** contains sildenafil.

FDA Jul/17: **EZ Weight Loss TX** is voluntarily recalling all lots of **La Bri's Body Health Atomic and Xplode capsules** to the consumer level since it was tainted with sibutramine.

FDA Jul/17:**Bestherbs Coffee LLC** is voluntarily recalling all lots of **New of Kopi Jantan Tradisional Natural Herbs Coffee**, 13 grams to the consumer level. FDA laboratory analysis confirmed the presence of desmethyl carbodenafil.

FDA Aug/17: warning parents and caregivers not to use "**Balguti Kesaria (or Kesaria Balguti) Ayurvedic Medicine**" due to the risk of lead poisoning.

FDA Aug/17: Man of Steel is voluntarily recalling 175 lots of **Man of Steel 1 and Man of Steel 2**, 4000mg at the retail level. The products have been found to contained undeclared Sildenafil.

FDA Aug/17: warning consumers not to drink **Longjack Coffee**, in addition to other instant coffee products that have been recalled recently – **Kopi Jantan Tradisional Natural Herbs Coffee, CaverFlo Coffee, and AMPT Coffee**. These products are made in Malaysia, and promoted and sold online for sexual enhancement. These products are labeled to contain instant coffee, non-dairy creamer, and other ingredients. However, FDA laboratory analysis confirmed: **CaverFlo Coffee and AMPT Coffee** contain undeclared sildenafil and tadalafil; **Longjack Coffee and Kopi Jantan Tradisional Natural Herbs Coffee** contain undeclared desmethyl carbodenafil, an analogue of sildenafil; and All of these products contain undeclared milk.

FDA Aug/17: Centurion Labs is voluntarily recalling 1 lot of **Ninjacof** (Lot# 200N1601) and 1 lot of **Ninjacof A** (Lot# 201NA1601) manufactured by Vilvet and distributed by Centurion Labs to the retail level due to potential contamination with Burkholderia cepacia.

FDA Aug/17 laboratory analysis confirmed that **Physic Candy – Curve & Physic Candy-Define** contains sibutramine.

FDA Sep/17: **Rhino 7, Papa Zen, Fifty Shades, and Grande X Dietary Supplements** by Gadget Island: Recall - Undeclared Drug Ingredients.The products have been found to contain undeclared Active Pharmaceutical Ingredients sildenafil, desmethyl carbodenafil and tadalafil.

FDA Sep/17: Natures Supplement, Inc. is voluntarily recalling 260 bottles of **Vegetable Vigra**, 200 mg capsules to the consumer level. FDA analysis found this product to be tainted with Sidenafil.

FDA Oct/17 laboratory analysis confirmed that **A1 Slim** contains sibutramine and phenolphthalein.

FDA Oct/17 laboratory analysis confirmed that **Tiger 5000** contains sildenafil and tadalafil.

FDA Oct/17 is reminding people to keep the **black licorice** in check. Eating 2 oz. a day for 2 weeks or more could lead to a cardiac arrhythmia in adults aged 40 and older. Glycyrrhizin, which comes from licorice root, can lead to a drop in potassium levels, the agency says. This, in turn, can result in arrhythmia, hypertension, edema, lethargy, and congestive heart failure.

FDA Oct/17 laboratory analysis confirmed that **Linsen Double Caulis Plus** (靈仙双藤素) contains dexamethasone.

FDA Nov/17 laboratory analysis confirmed that **Hard Times for Men** contains sildenafil.

FDA Nov/17 said it is aware of 36 deaths involving products made with **kratom** and hundreds of calls to poison control centers, which increased tenfold between 2010 and 2015. The FDA banned its importation in 2014, but in the years since, the agency has seized large amounts of kratom-containing dietary supplements.

FDA Nov/17 is investigating serious adverse events involving **Limbrel (flavocoxid),** a product in capsule form currently being marketed as a medical food to manage the metabolic processes associated with osteoarthritis. While a range of adverse events have been reported, two serious and potentially life-threatening medical conditions are among them: drug-induced liver injury and hypersensitivity pneumonitis.

FDA Dec/17 laboratory analysis confirmed that **Chao Jimengnan** contains sildenafil.

FDA Dec/17: Nutra Labs Inc. is voluntarily recalling lots sold by their firm of the male enhancement supplements **Bull 1800 mg Capsules** with the production date of 05/08/2016, and **Chao Jimengnan** 150 mg Tablets with Lot # 20151018 to the consumer level. FDA analysis found the products to be tainted with sildenafil, 0.026mg/capsule for Bull, and 70.46mg/tablet for Chao Jimengnan respectively.

FDA Dec/17: Marmex Corp is voluntarily recalling all lots of **Blue Pearl All Natural Male Enhancement Supplement**, 500mg to the consumer level. FDA analysis has found the products to contain sildenafil.

FDA Jan/18: **Flawless Beauty**, LLC is voluntarily recalling all lots of nineteen different products sold individually or as part of multi-unit kits alleged by the U.S. Food and Drug Administration ("FDA") to be misbranded or unapproved new drugs pursuant to the Federal Food, Drug, and Cosmetic Act. The FDA believes that these drugs present serious public health risks. All products were sold and distributed over the Internet to U.S. and foreign customers. All glutathione products were sold in multi-vial whitening kits, either alone or in combination with ampules of vitamin C and sterile water. Vials or ampules of vitamin C or sterile water purchased separately or as part of these whitening kits are also recalled.

FDA Jan/18: Arthri-D is recalling its Dietary Supplement "**Arthri-D 120ct**" Lot#1701-092 because it may be contaminated with Salmonella.

FDA Jan/18: Break Ventures/California Basics is recalling its Dietary Supplement "**Zero for Him 150ct**" Lot# 1710-638 because it may be contaminated with Salmonella.

FDA Mar/18: Bella All Natural is voluntarily recalling its **Diet Capsules labeled as Bella**, Lot Number MFD:10.15.2017 EXP: 10.14.2019, to the consumer level. This recall has been initiated due to presence of sibutramine.

FDA Mar/18:PDX Aromatics of Portland, Oregon DBA Kraken Kratom, Phytoextractum, and Soul Speciosa, has initiated a recall of certain **kratom-containing powder products** because it has the potential to be contaminated with Salmonella.

FDA Mar/18: Tamarack is voluntarily recalling Eclipse **Kratom-containing** powder products because it has the potential to be contaminated with Salmonella.

FDA Apr/18: issued a mandatory recall order for all food products containing powdered **kratom** manufactured, processed, packed, or held by Triangle Pharmanaturals LLC, after several were found to contain salmonella.
FDA Mar/18: laboratory analysis confirmed that **Black Lion Pill** contains sildenafil.
FDA Mar/18: laboratory analysis confirmed that **Red Zone Xtreme 3000 & Rhino 69 Extreme 50000** contains tadalafil.
FDA Apr/18: Club 13 is recalling **Maeng Da Red kratom powder**, since these products have the potential to be contaminated with Salmonella.
FDA Apr/18: Overland Park, KS, Epic Products, LLC is voluntarily recalling all lots of **Euphoric capsules**, packaged in 1 count blister cards, 3 count bottles, and 12 count bottles to the consumer level. FDA analysis found samples of Euphoric to be tainted with undeclared sildenafil and tadalafil,
FDA Apr/18: AMA Wholesale Inc. (Distributor/Re-seller), is voluntarily recalling **Rhino 69 Extreme 50000** capsules to the consumer level. FDA analysis found the product to be tainted with undeclared tadalafil.
FDA Apr/18: Viable Solutions of Nampa, ID has initiated a recall of certain **Kratom-containing powder products**, because it has the potential to be contaminated with Salmonella.
FDA Apr/18: NGB Corp. of West Jordan, Utah is voluntarily recalling **NxtGen Botanicals Maeng Da Kratom** labeled bottles of encapsulated product because it has the potential to be contaminated with Salmonella
FDA May/18: MBI Distributing, Inc. is voluntarily recalling all lots of homeopathic Teething Drops, Nausea Drops, Intestinal Colic Drops, Stomach Calm, Expectorant Cough Syrup, Silver-Zinc Throat Spray, and Argentum Elixir, within expiry, to the consumer level. The drug products have been found to be manufactured with a lack of adequate controls.
FDA May/18: 7K and Poseidon 4500 by Shoreside Enterprises: Voluntary Recall - Due to Presence of Undeclared Sildenafil and Tadalafil.
FDA May/18: Herb-X Solutions X-Jow Pain Gel is used as an external analgesic and the United Exchange Acne Shave Moisturizer and Acne Shave Shave Cream with Acne. FDA Jun/18: Homeopathic Teething Drops, Nausea Drops, Intestinal Colic Drops, Stomach Calm, Expectorant Cough Syrup, Silver-Zinc Throat Spray, and Argentum Elixir by
FDA Jun/18: **Kratom (mitragyna speciosa**) Powder Products by Gaia Ethnobotanical: Recall - Due to **Potential Salmonella Contamination**
FDA Jul/18: **Blissful Remedies**., is voluntarily **recalling only Lot No.: 112710** with expiration 03/2019 found embedded on the top of package of **kratom (*mitragyn a speciosa*) powder products**, it manufactured, processed, packed, and/or held, between "March 1, 2018" to "April 30, 2018" to the consumer level. The products have been found by the U.S. Food and Drug Administration ("FDA") via sample testing to have **salmonella contamination**.
FDA July/18: laboratory analysis confirmed that **Maximum Powerful contains sildenafil**.
FDA Jul/18: laboratory analysis confirmed that **Grakcu Capsule, C.U. Plus, Dale Mas contains sildenafil and tadalafil**.
FDA Jul/18: laboratory analysis confirmed that **Asunsa contains sibutramine, N-desmethylsibutramine, benzylsibutramine, phenolphthalein and diclofenac**.
FDA July/18: laboratory analysis confirmed that **Lyn DTOX FS3 contains sibutramine and N-desmethylsibutramine**.
FDA Aug/18: is **advising consumers not to purchase or use Nuvitra**, a product promoted for weight loss. This product was identified during an examination of international mail shipments. FDA laboratory analysis confirmed that Nuvitra contains **sibutramine and fluoxetine.**
FDA Aug/18: **laboratory analysis confirmed that XXXPlosion Ultra, Ding Ji Wei Ge, 5K & Panther Power Platinum 11000 contains sildenafil**.
FDA Sep/18: laboratory analysis confirmed that **Extenze Nutritional Supplement, Extenze Plus, PremierZen Gold 4000 contains sildenafil**.
FDA Sep/18: laboratory analysis confirmed that **Slimming Capsule contains sibutramine and phenolphthalein**.
FDA Sep/18: laboratory analysis confirmed that **BodySlim Herbal & Easy 2 Slim contains sibutramine**.
FDA Oct/18: laboratory analysis confirmed that **ProSolution, V-Max, USA for Women, Strong Horses & FX75000 contains sildenafil**.
FDA Oct/18: laboratory analysis confirmed that **Green Lean Body Capsule * Baschi Quick Slimming Capsule contains sibutramine and N-desmethylsibutramine**.
FDA Oct/18: laboratory analysis confirmed that **Shengan Natural Model, Like Slim Coffee & In Shape contains sibutramine**.
FDA Nov/18: Several samples of the **botanical kratom have tested positive for nickel and lead at levels not safe for humans**, according to recent analyses done by the FDA. Some people use kratom, which contains opioids, to self-treat opioid addiction and other conditions. The tests of 26 kratom products were conducted as part of the agency's investigation into a salmonella outbreak associated with kratom. The levels of nickel and lead detected aren't likely to induce heavy metal poisoning from a single use, the FDA said, but they could with chronic use.
FDA Dec/18: **laboratory analysis confirmed that MOB Candy & Willy Go Wild contains sildenafil and tadalafil**.
FDA Jan/19: laboratory analysis confirmed that **The Silver Bullet** contains sildenafil and tadalafil.
FDA Jan/19: laboratory analysis confirmed that **Slimina** contains sibutramine.
FDA Jan/19: laboratory analysis confirmed that **GoLean Detox & Slimmer Extreme Thermogenic Formula** contains sibutramine and phenolphthalein.
FDA Jan/19: laboratory analysis confirmed that **Ultra Fit, 1 Day Diet** contains sibutramine and N-desmethylsibutramine.
FDA Jan/19: laboratory analysis confirmed that **Red Stallion Extra Strong** contains tadalafil.
FDA Jan/19: laboratory analysis confirmed that **Natural V=GRA, Yong Gang, Silver Bullet 10x & Black King Kong** contains sildenafil and tadalafil.
FDA Jan/19: laboratory analysis confirmed that **Golden Ant, Instinct Best Sexual Enjoyment & Nectar Del Amor** contains sildenafil.
FDA Jan/19: laboratory analysis confirmed that **Slim Bio Capsules** contain sibutramine, N-desmethylsibutramine, sildenafil, tadalafil, benproperine and diphenhydramine.
FDA Feb/19: **GoLean Detox Capsules** by GoLean Detox USA: Recall - Due to Presence of Undeclared Sibutramine and Phenolphthalein.
FDA Mar/19**:** Select **Kratom Products** by Sunstone Organics: Recall - Due to Potential Contamination by Salmonella.
FDA Apr/19: **Aphrodisiac Capsules** by SD Import: Recall - Due to Presence of Undeclared Sildenafil.
FDA Apr/19: **BLUEFUSION Capsules** by Ata Int.: Recall - Due to Presence of Undeclared Sildenafil, Tadalafil, Desmethyl Carbodenafil, Dithiodesmethyl Carbodenafil, Scutellarin and Daidzein
FDA May/19: The **Beast Capsules by STIFF BOY**: Recall - Due to Presence of Undeclared Sildenafil
FDA May/19: laboratory analysis confirmed that **Man Fuel Shooter (Tropical Fruit Flavor) contains tadalafil and desmethyl carbodenafil**.
FDA May/19: laboratory analysis confirmed that **Man Fuel Xtreme Edition contains sildenafil, dithiodesmethyl carbodenafil and desmethyl carbodenafil**.
FDA Jun/19: laboratory analysis confirmed that **Peru Maca & Germany Black Gorilla** contains sildenafil.
FDA Jun/19: laboratory analysis confirmed that **Adelgasin Plus, Lishou Fuling Jiaonang & Absolute Nine Slim** contains sibutramine and N-desmethyl sibutramine.
FDA Jun/19: laboratory analysis confirmed that **Super Slimming Herb & Detoxi Slim** contains sibutramine.
FDA July/19: laboratory analysis confirmed that **Black Storm, Big Penis, Boss Lion 9000, De Guo Heijin Gang, Herb Viagra, La Pepa Negra, Odimafo Powerful Tablet 200 mg, Plant Vigra, Shengjingpian, & Vigour 800mg** contains sildenafil.
FDA July/19: laboratory analysis confirmed that **Reduktis Max** contains sibutramine.
FDA Sep/19: laboratory analysis confirmed that **Love in S** contains sibutramine and N-desmethylsibutramine.
FDA Sep/19: laboratory analysis confirmed that **Sheaya Lender** contains sibutramine and fluoxetine.
FDA Sep/19: laboratory analysis confirmed that **Mero Macho** contains tadalafil.
FDA Sep/19: laboratory analysis confirmed that **LOBO** contains sildenafil.
FDA Sep/19: laboratory analysis confirmed that **Anaconda Strong Formula, La Pepa Negra, & Lung Leader** contains sildenafil.
FDA Sep/19: Fitoterapia is voluntarily **recalling Mero Macho Artificial Passion Fruit Flavored Vitamin C Liquid Supplement** to the consumer level. FDA analysis has found the product to be tainted with tadalafil.
FDA Oct/19: laboratory analysis confirmed that **Skinny Pill** contains undeclared DMAA, also known as 1,3-dimethylamylamine or methylhexanamine.
FDA Oct/19: **Green Lumber** (dietary supplements for male sexual enhancement) Capsule Packages by GL Holdings: Recall - Due to Presence of Undeclared Tadalafil
FDA Nov/19: **Up2** by Med Man Distribution: Recall - Due to Presence of Undeclared Sildenafil.
FDA Nov/19 laboratory analysis confirmed that **Man Erect & SHENGDA & Silver Bullet** (10 Male Enhancement Capsules) contains sildenafil.
FDA Nov/19 reminds consumers not to purchase or use **Power Khan**. An FDA laboratory tested additional samples of Power Khan and found it contained desmethyl thiosildenafil, thioaildenafil, and aildenafil.
FDA Dec/19: laboratory analysis confirmed that **PremierZEN Gold 7000** contains sildenafil and tadalafil.
FDA Dec/19: laboratory analysis confirmed that **U-Dream Full Night & U-Dream Lite** contains a substance structurally similar to eszopiclone and zopiclone.
FDA Dec/19: analysis has found **Bull Platinum 30000, Stallion Platinum 30000, Rhino 7 Platinum 30000, and Panther Platinum 30000** to be tainted with undeclared tadalafil.
FDA Feb/2020: laboratory analysis confirmed that **OrgaZEN Gold 5800** contains sildenafil.
FDA Feb/2020: laboratory analysis confirmed that **Alpha-Male, XXX Platinum WOODIE** contains sildenafil and tadalafil.

FDA Feb/2020: laboratory analysis confirmed **RMFLEX** contains diclofenac.
FDA Feb/2020: **Up2 and Bow & Arrow** by Med Man: Recall - Due to Presence of Undeclared Sildenafil.
FDA Mar/2020: **Active male** contains tadalafil.
FDA Mar/2020: Natural Remedy Store is voluntarily recalling all lots of **Active Male, 500mg** capsules to the consumer level.
FDA Apr/20: laboratory analysis confirmed that **Black Mamba Premium 18000** contains tadalafil.
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.
Healh 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 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.
Health Canada Dec/16 is advising Canadians that the unauthorized product "**Control-Max**" may pose serious health risks as it is labelled to contain a prescription drug (yohimbine).
Health Canada Dec/16 is advising Canadians that three unauthorized products, "**Lithium Plus, Serotonin Support, and Brain Support**," may pose serious health risks because they may contain the prescription drug Lithium Orotate.
Health Canada Jan/17 is advising Canadians that it has seized the unauthorized health product "**Blow**", by Limitless Pharma, from Atomik Nutrition at 450 Boulevard de Mortagne, Boucherville, QC. "Blow" is promoted as a pre-workout supplement and is labelled to contain the unauthorized drug 1,3 Dimethylamylamine (DMAA), which may pose serious health risks such as high blood pressure and stroke.
Health Canada Jan/17 is advising Canadians that it has seized unauthorized health products being sold at 24 Hour Adult Mart on Yonge St., Toronto, ON. Three of the seized products are "**poppers**" labelled to contain alkyl nitrites.
Health Canada Jan/17 is advising Canadians that it has seized three unauthorized workout supplements from Reflex Supplements at #105–10712, 78 Ave., Grande Prairie, AB. "**Animal PM**" is labelled to contain L-dopa while "**Blade**" is labelled to contain yohimbine.
Health Canada Feb/17 is advising Canadians that a safety review has found a risk of serious skin burns with the use of certain over-the-counter (OTC) topical pain relievers containing **menthol**.

Health Canada Feb/17 is advising Canadians that it has seized unauthorized health products promoted as workout, weight loss and dietary supplements from **Atomik Nutrition** at 102-90 Boul. Saint-Jean-Baptiste, Châteauguay, QC (see table below). The products are labelled to contain various drugs, including prescription and controlled drugs, **Dymethazine**: Osmo Pharma-17ß–hydroxy–2α,17–dimethyl–5α–androstan–3–one azine; **DHEA**: Osmo Pharma- Dehydroepiandrosterone (DHEA); **Amped**:Osmo Pharma-Corynanthe Extract (Pausinystalia Yohimbe Bark); **Exo-13 Exothermic Fatburner**: Prime Nutrition-1,3-Dimethylamylamine, Caffeine Anhydrous, Yohimbine HCl, Bitter Orange Extract 30%; **Insane Cutz**: Insane Labz-Rauwolfia Vomitoria Extract (std. min. 90% alpha Yohimbine); **Yohimbine HCl**:Primaforce-Yohimbine HCl; & **Dust Extreme**: Blackstone Labs- 1,3 DMAA (Dimethylamylamine), Caffeine Anhydrous.

Health Canada Mar/17: 90° **Jiushidu Capsules, African Viagra, Big Penis Male Sexual Stimulant, Black Mamba 2 Premium, Black 3K Plus Male Sexual Enhancement Capsules, Bl4ck 4K Capsules, Duramaxxx, Power Male Sexual Stimulant, Rhino 5 1500 Capsules, Rhino 7K 9000 Male Performance Booster, Rhino 8 Platinum 8000, Rhino 9 Premium 3500 & Triple Green Capsules** contains undeclared sildenafil.

Health Canada Mar/17: **Megajex Natural Male Sex Enhancer Dietary Supplement** contains undeclared sildenafil & tadalafil.

Health Canada Mar/17: **Queen Slimming Soft Gel** contains undeclared sibutramine

Health Canada Mar/17: **VIP Bio Mangosteen Complex** contains undeclared sibutramine & phenolphthalein.

Health Canada Mar/17 is advising Canadians that the unauthorized health product "**PureCare Herbal Cream**" may pose serious health risks. The product is promoted as a natural treatment for eczema and psoriasis in children and babies. Health Canada testing confirmed the presence of a prescription steroid (clobetasol propionate) and another ingredient (phenoxylethanol) not declared on the product label.

Health Canada Mar/17: **Chao Jimengnan Super Powerful Man Tablets & Zhen Gongfu capsules** has undeclared sildenafil by the Australian Therapeutic Goods Administration.

Health Canada Mar/17: **GoldReallas Original & GoldReallas XXX** has undeclared sildenafil & thiosildenafil by the FDA.

Health Canada Mar/17: **Impeous Man capsules** has undeclared sildenafil & phenolphthalein by the Australian Therapeutic Goods Administration.

Health Canada Mar/17: **Old Chinese & Shenjingpian** has undeclared sildenafil by the FDA.

Health Canada Mar/17: **XtraHRD** has undeclared N-desmethyl tadalafil by the FDA.

Health Canada Mar/17: **CA NI Slim BELLANCE** has undeclared orlistat by the Hong Kong Department of Health.

Health Canada Mar/17: **Lean Extreme Max & X-treme Beauty Slim** has undeclared sibutramine by the FDA.

Health Canada Mar/17: **Platinum Max Strength Blue Pill Version, Slimming Plus Advanced & Platinum Weight Loss Solution** has undeclared sibutramine & phenolphthalein by the FDA.

Health Canada Mar/17 is advising Canadians that it has seized multiple unauthorized health products from three retailers in Ontario (see table below). The products are promoted for sexual enhancement and were found to contain, or are labelled to contain, prescription drugs that may pose serious risks to the health of Canadians. Hespeler Road Adult SuperStore (261 Hespeler Road, Cambridge ON): **LipsTenZen, Super Panther 7K & Thunder Bull 7K** contains Yohimbe. **One More Knight** contains tadalafil and dapoxetine. **MV7 Days 2000** contains sildenafil and tadalafil. Naughty Shop (330 Wellington Rd. S, London ON): **LipsTenZen, Super Panther 7K & Triple Green** contains Yohimbe. VXI Multimedia (800 Petrolia Road, Unit 18, Toronto, ON): **Opti-Sildenafil** 100 mg contains sildenafil, **Opti-Tadalafil** 20 mg contains tadalafil.

Health Canada Apr/17 is advising Canadians that it has seized the unauthorized injectable health product "**Botulax**" and unauthorized medical sutures "**The Lift II**" from SPMU-MTS Studio, at 8788 McKim Way, Unit 1200, in Richmond, BC. Both products may pose serious risks to the health of Canadians.

Health Canada Apr/17 is advising Canadians that the unauthorized health product "**Rhino Blitz Gold**" may pose serious health risks, after testing confirmed it contains an undeclared prescription drug (sildenafil).

Health Canada Apr/17 is warning Canadians about unauthorized health products, including unauthorized prescription drugs, sold **online at sarms.ca.**

Health Canada Apr/17 laboratory tests have confirmed that two additional unauthorized products seized from **24 Hour Adult Mart in Toronto** contain undeclared tadalafil.

Health Canada May/17 is advising Canadians that it has seized the unauthorized health product "**Dust Extreme**" by Blackstone Labs, from Minotaure Nutrition, in Terrebonne, QC. "Dust Extreme" is promoted as a pre-workout supplement and is labelled to contain the unauthorized drug 1,3 Dimethylamylamine (DMAA).

Health Canada May/17 is advising Canadians that it has identified two unauthorized health products, "**Super Panther 7K**" and "**Triple Green**," sold at Rixxx Adult Store at 2839 Saint Joseph Boulevard in Ottawa, ON. The products are promoted for sexual enhancement and are labelled to contain yohimbe.

Health Canada May/17: **Africa Black Ant capsules & Australia Kangaroo Essence** by Australia Therapeutic Goods Administration has undeclared sildenafil.

Health Canada May/17: **Arouse-Plus & Bazook Bullet** by FDA has undeclared tadalafil.

Health Canada May/17: **Anyang Herbal Blue** by Singapore Health Sciences Authority has undeclared sibutramine.

Health Canada May/17: **Anyang Herbal Red** by Singapore Health Sciences Authority has undeclared diclofenac, phenolphthalein, and sibutramine.

Health Canada May/17: **Change Me Herbal Slimming Capsules & Ultimate & Herbal Slim Weight Loss capsules** by Australia Therapeutic Goods Administration has undeclared sibutramine.

Health Canada May/17: **Placebo tablets** by Australia Therapeutic Goods Administration has undeclared clenbuterol.

Health Canada May/17 is advising Canadians that the unauthorized health products "**Black Mamba 2 Premium**" and "**ExtenZe**" are labelled to contain drugs that may pose serious health risks (DHEA, pregnenolone, and yohimbe/yohimbine).

Health Canada May/17 is advising Canadians that **Garnoff Botanicals** is voluntarily recalling unauthorized "High By Nature" kratom products (Mitragyna speciosa) because they may pose serious health risks when swallowed or inhaled.

Health Canada May/17 is advising Canadians that multiple unauthorized health products seized from **two retailers in Scarbofrough, ON**, may pose serious risks to health. Products seized include "poppers" and products promoted for sexual enhancement. Adult Store 2365 Eglinton Ave E Scarborough ON had Rochfort 10mL-Isobutyl nitrite; Finegra-100-Sildenafil; Super Panther 7K-Yohimbe; Premium X Pulse 2000-Yohimbe; Premium Pro Power 3500-Yohimbe bark extract; Hard Rock 3800-Yohimbe bark extract; XXL Ant 3000-Yohimbe bark extract; Black Mamba 2 Premium-Yohimbe; Mamba is Hero-Yohimbe, sildenafil, desmethyl carbodenafil and dapoxetine; Master Zone 1500- Sildenafil and tadalafil. Homerama Adult Video 2524 Eglinton Ave E Scarborough had ONWet XXX-Yohimbe; 7K-Yohimbe; Super Panther 7K-Yohimbe; Passion Classic- Yohimbe; Titanium 4000-Sildenafil and tadalafil. Adult Store 2365 Eglinton Ave E Scarborough ON had Zhen Gongfu-previous testing of product with similar packaging, identified as containing undeclared sildenafil; Stiff Rock- previous testing of product with similar packaging, identified as containing undeclared sildenafil; One For Her- previous testing of product with similar packaging, identified as containing undeclared tadalafil; Rush 10mL, Super Rush 10mL & Blue Boy 10mL-previously seized products with similar packaging were labelled to contain alkyl nitrites. Homerama Adult Video 2524 Eglinton Ave E Scarborough ON had Rush 10mL, Super Rush 10ml, Jungle Juice Gold Label 10mL, Jungle Juice Gold Label 30mL, Jungle Juice Platinum 10mL, & Jungle Juice Platinum 30mL previously seized products with similar packaging were labelled to contain alkyl nitrites.

Health Canada May/17 is advising Canadians that multiple unauthorized products labelled to contain **L-tryptophan or lithium orotate** were being sold on amazon.ca, and may pose serious health risks.

Health Canada Jun/17 is advising Canadians that RGR Canada Inc. is voluntarily recalling unauthorized "**Matrix Red Vein Thai**," "**Matrix White Vein Thai**" and "**Medicine Man Lone Wolf**" **kratom** capsules.

Health Canada June/17: **VENERGY Capsule** 100mg has undeclared sildenafil by the Hong Kong Department of Health.

Health Canada June/17: **Nangen Zengzhangsu** undeclared sildenafil by Australia Therapeutic Goods Administration.

Health Canada June/17: **Lose Weight capsules** has undeclared sibutramine and diclofenac by Australia Therapeutic Goods Administration.

Health Canada June/17: **Slim-Vie Slimming Capsules** has undeclared sibutramine, sildenafil, and phenolphthalein by Australia Therapeutic Goods Administration.

Health Canada June/17: **PHQ 1001 Khasiat Penawar Herba Qaseh Serata Herb** has undeclared dexamethasone, piroxicam, griseofulvin and paracetamol by Singapore Health Sciences Authority.

Health Canada June/17: **TONIK TUAN HAJI 1921** has undeclared dexamethasone by Hong Kong Department of Health.

Health Canada Jun/17 is advising Canadians that the unauthorized sexual enhancement product "**Super Panther 7K,"** labeled to contain a drug (yohimbe).

Health Canada Jun/17 is advising Canadians that it has seized unauthorized "**Jupiter**" and "**Kratom Zone**" kratom products from two retail stores in Edmonton, AB. Kratom may pose serious health risks when swallowed or inhaled.

Health Canada Jun/17 is advising Canadians that the unauthorized sexual enhancement product "**Rhino 69 Extreme 10K**" may pose serious health risks because its label says that it contains a prescription drug (yohimbe extract (bark)).

Health Canada Jul/17 is advising Canadians that it has seized several unauthorized **kratom products from Culture Rising** at 1248 Main St E, Milton, ON.

Health Canada Jul/17 is advising Canadians that the unauthorized sexual enhancement product "**Black Mamba Premium**" may pose serious health risks because its label says it contains a drug called yohimbe.

Health Canada July/17 is advising Canadians that the unauthorized natural health product promoted as a workout supplement "**Fluffy Unicorn**" may pose serious health risks.

Health Canada laboratory testing found that the product contains undeclared synephrine, and higher levels of caffeine than declared on the label.
Health Canada Jul/17: **Man XXX** has undeclared levodopa by the Australia Therapeutic Goods Administration.
Health Canada Jul/17: **Big N Hard** has undeclared tadalafil by the United States Food and Drug Administration.
Health Canada Jul/17: **Black Gorilla, Maxman IV, Maxman Premium, Maxman V, MMC Maxman XI, New Advanced Technological, V9 Male Sexual Stimulant, Real Skill Male Sexual Stimulant, & Rize N Shine** has undeclared sildenafil by the Australia Therapeutic Goods Administration.
Health Canada Jul/17: **Cummor & Monkey Business** has undeclared N-desmethyl tadalafil by the United States Food and Drug Administration.
Health Canada Jul/17: **Dragon Max, Oh Baby!, & XXXL Penis Enlarging Ointment** has undeclared tadalafil by the Australia Therapeutic Goods Administration.
Health Canada Jul/17: **Tornado** has undeclared nortadalafil by the United States Food and Drug Administration.
Health Canada Jul/17: **Xrect** has undeclared tadalafil and descarbonsildenafil by the United States Food and Drug Administration.
Health Canada Jul/17: **Z Daily** has undeclared homosildenafil by the United States Food and Drug Administration.
Health Canada aug/17 is advising Canadians that "**Selekta Pregnenolone**," an unauthorized prescription product sold online at www.antyler.com, may pose serious health risks.
Health Canada Nov/17: review concluded that there may be a link between the use of **green tea extract** and a risk of rare and unpredictable liver injury.
Health Canada Mar/18 is advising Canadians that **Sisu Inc. has voluntarily recalled numerous natural health products because the glass bottles** that the products are packaged in may contain glass fragments.
Health Canada Mar/18 is advising Canadians that "**Beyond Yourself Multi Athlete**" multivitamin and unauthorized "Multi-Vitamines" sold in bulk were seized from several Shop Santé stores in Quebec because they may pose serious health risks.
Health Canada Mar/18: is advising Canadians that two versions of the sexual enhancement product "**Leopard Miracle of Honey**" may pose serious health risks. Both versions are labelled as being approved by Health Canada, with NPN 80073650. Health Canada's testing found that both versions of the product contain the undeclared prescription drug sildenafil.
Health Canada Apr/18: is advising Canadians that one lot of "**Organic Traditions Shatavari Powder**" is being voluntarily recalled by Advantage Health Matters Inc. Company testing found Salmonella bacteria contamination.
Health Canada Apr/18: One lot of Traditional Medicinals "**Throat Coat Lemon Echinacea**" herbal tea recalled because of potential contamination with Salmonella
Health Canada May/18 has seized four unauthorized drugs from Gigi's Market, 23 Montreal Road, Ottawa, ON. The products (Ampicillin, Kamox, Medampi and Medomox) are labelled to contain antibiotic drugs (ampicillin or amoxicillin) that can only be dispensed by a healthcare professional to a patient with a valid prescription.
Health Canada May/18 is advising Canadians that it has seized an unauthorized "Botox" product and other unauthorized health products from Arshia Hair Salon and Spa (6062A Yonge Street) in Toronto, ON, because they may pose serious health risks
Health Canada Aug/18: testing **of Jian Pai Natural Skin Care Cream, also called ''Yikangshuang," found that it contains two antifungal drugs (fluconazole and miconazole)** that are not listed on the product label.
Health Canada Sep/18: Canadians should not buy or use health products that contain 2,4-dinitrophenol, more commonly known as **DNP**, because it is toxic and can cause death. Products containing DNP are primarily marketed towards bodybuilders and are promoted online as a "fat burner" or "shredder" and for weight loss.
Health Canada Nov/18 is advising Canadians that **two versions of "Vita-X Revitalizing Capsules" by Lanlay Healthmetic Inc**., promoted for "long lasting vital energy for men," **may pose serious health risks & may contain sildenafil.**
Health Canada Jan/19: inspectors have seized products, ingredients and equipment from A1 Herbal Ayurvedic Clinic Ltd. in Surrey, British Columbia (31-8430, 128 Street), and from an affiliated clinic in Brampton, Ontario (11-351 Parkhurst Square). The seizures came after the British Columbia Centre for Disease Control informed Health Canada of **a case of heavy metal toxicity** involving a patient who was using products from the Surrey clinic. Laboratory testing identified lead and mercury in the products.
Health Canada Jan/19: **Quizz capsules** contain undeclared lead & mercury.
Health Canada July/19: Hepatotoxicity associated with the use of **oral Aloe vera**-containing health products.
Health Canada Nov/19: is advising Canadians that **Passion X & Passion Fem** contains undeclared sildenafil.
Health Canada Nov/19: testing of some of the **Ayurvedic products** from the clinic (Dutta Health Centre-Ayurvedic Clinic in Surrey, B.C.,) found that they contained high levels of lead and mercury.
Health Canada Feb 2020: laboratory testing found that **Performance Plus capsules & Never Rest** contains a prescription drug 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
Melchart D, Linde K, Fischer P, **Echinacea** for preventing and treating the **common cold**. Cochrane Database Syst Rev. 2000;(2):CD000530. CONCLUSIONS: The majority of the available studies report positive results. However there is not enough evidence to recommend a specific Echinacea product, or Echinacea preparations for the treatment or prevention of common colds.
MHRA Aug 2011 issues warning over traditional Chinese medicines containing **Lei Gong Teng (tripterygium wilfordii)**
MHRA Dec/11Health Sciences Authority in Singapore has issued a press release warning the public of four adulterated health products. **ATHRI-Eze** - is marketed as a traditional Chinese medicine and packaged in a bottle of 20 white capsules. **SEAR HEANG TIENCHI TU CHUNG WAN** - claims to treat rheumatic pain and backache and is sold in a bottle of 40 black pills with a red label. **CAP WIJAYA KUSUMA (AN KI IT)** and **WIKU JAHE KENCUR (AKUR MUJARAB)** - are promoted as Malay Jamu (postnatal) medicines, which are packed in foil sachets of brown powder and are labelled to treat rheumatoid and arthritic conditions.These four products have been found to contain undeclared pharmaceutical medicines. Ingredients found include: dexamethasone, furosemide, paracetamol, chlorpheniramine (also known as chlorphenamine), phenylbutazone, allopurinol & prednisolone.
MHRA Dec/11 In response to an urgent notice issued by MHRA, Bee Health Ltd has agreed to stop marketing FSC Black Cohosh 1000 mg due to concerns about the high dosage of black cohosh in the product. The MHRA advises consumers not to take the FSC Black Cohosh product as it equates to 50 times the dose approved for traditional herbal medicinal products used to relieve menopausal symptoms. It is not known what the risks or effects on the body could be associated with such a high level of Black Cohosh.
MHRA Jan/12 Consumers are advised not to take unlicensed **Butterbur (Petasites hybridus)** herbal remedies. Butterbur contains pyrrolizidine alkaloids (PAs) which studies have shown can result in serious liver damage and organ failure. PAs have also been shown to lead to cancer in animals. Butterbur is most commonly used to treat migraine and hayfever. Butterbur products have been associated with cases of liver toxicity; 40 cases have been reported in the literature. Of these cases, nine were of acute hepatitis and two of the nine cases resulted in liver failure requiring transplantation. The cases of liver toxicity appear to have occurred with extracts of Butterbur where the PAs had been removed and only small amounts remained. There is some evidence that other constituents found in Butterbur such as the sesquiterpene constituents for example petasin may be implicated in the liver toxicity.
MHRA Feb/12 Herbal sliming products found to contain potentially dangerous undeclared pharmaceuticals: **Expelling Grease Slimming Abdomen, V12 Fruit Slimming, 100% Natural Weight Loss Coffee, Leisure 18 Slimming Orange Juice, Fashion Slimming Milk Shake, Langli, Ya Buk & Fruit and vegetables lose weight**. MHRA has received advice from the Danish Medicines Agency that these unlicensed products have been tested and found to contain the Prescription Only Medicine Sibutramine.
MHRA Feb/12 has received advice from AGES PharmMed in Austria and the Danish Medicines Agency, warning that these unlicensed products have been tested and found to contain Tadalafil and/or Sildenafil: **AH Free/Reflexit, Stree Overlord, Man King, VigRX, Maxman, Maxman III, Viriya, & Imbiza for Men.**
MHRA Feb/12 Following a safety alert issued in October 2010 about slimming products containing Paiyouji the Agency has received a further complaint about a product called **'Paiyouji Plus - Fast Acting Slimming Tea'**. This product has been tested by the Agency and, as in the case of other Paiyouji products, found to contain sibutramine.
MHRA Mar/12 Traditional Chinese Medicine (TCM) **Anshen Bunao Pian** (Chung Lien Kulin Brand) has been found by the Department of Health in Hong Kong to contain 55 times the level of mercury permitted in China. Acute mercury poisoning can damage the neurological system and kidneys. The product is manufactured in mainland China and imported by Fung Wah (HK) Company.
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.

MHRA Mar/18: **Yiganerjing Cream** are urged to discontinue use immediately as it contains an undisclosed steroid and two antifungal ingredients.

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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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safe adjunctive treatment strategy for SRI nonresponders with major depressive disorder and warrant replication.
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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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Additional information about MIRCERA (Web-only)

Methoxy polyethylene glycol-epoetin beta **MIRCERA** [8] Single-dose **vials** (solution): 50, 100, 200, 300, 400, 600, 1000 mcg/mL Single-dose **pre-filled syringes:** 50mcg/0.3mL, 75mcg/0.3mL, 100mcg/0.3mL, 150mcg/0.3mL, 200mcg/0.3mL, 250mcg/0.3mL, 400mcg/0.6mL, 600mcg/0.6mL	✓ **Anemia of CKD** Pre-filled syringes: sterile & do not contain preservatives. **Storage**: 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.		Subcut in ND-CKD & PD-CKD; **IV** or subcut in HD-CKD Not currently on ESA tx: 0.6 mcg/kg every 2 weeks as a single IV or subcut inj Pts on ESA: can convert to MIRCERA given once a month as a single IV or subcut inj. Monthly Mircera starting IV or subcut 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 subcut. 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 avail. in Canada, NOC received Mar 2008

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FDA Feb/10 and Amgen notified healthcare professionals and patients that all ESAs must be used under a REMS risk management program. As part of the risk management program, a Medication Guide explaining the risks and benefits of ESAs must be provided to all patients receiving an ESA. Under the ESA APPRISE Oncology program, Amgen will ensure that only those hospitals and healthcare professionals who have enrolled and completed training in the program will prescribe and dispense ESAs to patients with cancer. Amgen is also required to oversee and monitor the program to ensure that hospitals and healthcare professionals are fully compliant with all aspects of the program. FDA is requiring a REMS because studies show that ESAs can increase the risk of tumor growth and shorten survival in patients with cancer who use these products. Studies also show that ESAs can increase the risk of heart attack, heart failure, stroke or blood clots in patients who use these drugs for other conditions.

FDA June/11 notified healthcare professionals that new, modified recommendations for more conservative dosing of Erythropoiesis-Stimulating Agents (ESAs) in patients with chronic kidney disease (CKD) have been approved to improve the safe use of these drugs. FDA has made these recommendations because of data showing increased risks of cardiovascular events with ESAs in this patient population. The new dosing recommendations are based on clinical trials showing that using <u>**ESAs to target a hemoglobin level of greater than 11 g/dL in patients with CKD provides no additional benefit**</u> 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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IRON MANAGEMENT: Online Extras

Red Cell Indices	Laboratory Investigations	Findings	Differential Diagnosis
MCV <80 fL **Microcytic** anemia	Serum **ferritin** preferred, serum iron, TIBC, RDW (Ferritin: is an acute phase reactant that may be ↑ if concurrent liver congestion/dx, collagen dx, malignancy, infection or inflammation	**Ferritin** <20mcg/L ⇒ **Ferritin** >20mcg/L ⇒	Iron deficiency anemia (IDA) high RDW, low-normal reticulocyte, low serum iron with high TIBC, ↑ transferrin, ↓ transferrin saturation & ferritin. Anemia chronic dx normal-↑ RDW, low serum iron, low-normal TIBC & transferrin saturation, only ~25% microcytic, Hemoglobinopathy, Lead Overload , Thalassemia normal TIBC, normal to ↑ serum iron & transferrin saturation major high RDW & minor normal RDW; Sideroblastic anemia ↑RDW
MCV 80-100 fL **Normocytic** anemia	Consider loss of blood, **reticulocyte** count	**Blood loss**, Hemolysis ⇒ No blood loss ⇒	Treat cause GI or menstrual bleed (Use of ASA/NSAIDs, warfarin etc.), high reticulocyte Anemia of chronic dx normal-↑RDW, low serum iron, low-normal TIBC, ↓or normal transferrin, normal- ↑ferritin; **Tx disease**, ?transfusion,?Epo & not iron if ↑ or normal ferritin. Aplastic anemia, Mixed deficiency anemia, Endocrine hypothyroidism, Hemoglobinopathy
MCV >100 fL **Macrocytic** anemia	Consider loss of blood, reticulocyte count, vitamin B_{12} & folate level, **Blood film,** TSH, LFTs	Blood loss ⇒ No Blood loss ⇒	Treat cause GI or menstrual bleed (Use of ASA/NSAIDs, warfarin etc.), high reticulocyte Liver dx normal RDW, Myelodysplasia high RDW, Folate or Vit B_{12} deficiency high RDW, low-normal reticulocyte, Hemolytic anemia

Examples of Iron Deficiency Anemia Causes & Types:			
↑ blood loss	**↓ iron intake/absorption/availability**	**↑ RBC destruction**	**↑ demand**
e.g. from dialyzer, phlebotomies, esophageal/ GI/uterine/anal bleed, epistaxis, hematuria, IBD	e.g. gastric/bariatric surgeries e.g. gastric resection, Roux-en-Y, biliopancreatic diversion, poor diet Cows milk -infancy, obesity, diarrhea, intestinal inflammation/celiac dz/H pylori, food interactions, ↓ erythropoietin synthesis in CKD, 2° hyperparathyroidism in dialysis	e.g. hemolysis	e.g. of ESA tx, pregnancy, physical growth

Medication Causes of anemia:				
Iron Deficiency Anemia:	**Aplastic anemia:**	**Hemolysis in G6PD Deficiency:**	**Hemolytic anemia:**	**Megaloblastic anemia:**
anticoagulants, NSAIDs, aspirin, PPIs, laxatives, corticosteroids, phosphate chelators.	allopurinol, antithyroid meds, chemo, chloramphenicol, chlorpromazine, clopidogrel, corticosteroids, furosemide, gold, indomethacin, interferon α2a&2b, isoniazid, methyldopa, NSAIDs, penicillamine, phenothiazines, procainamide, sulfonamides & ticlopidine.	ascorbic acid, benzocaine, chloroquine, dapsone, hydroxychloroquine, nitrofurantoin, phenazopyridine, primaquine, sulfacetamide, sulfamethoxazole, sulfanilamide & sulfapyridine.	ACEI, acetaminophen, ASA/NSAIDs, cephalosporins, chlorpromazine, chlorpropamide, diclofenac, hydrochlorothiazide, interferon α2a&2b, isoniazid, levodopa, levofloxacin, mefenamic acid, methadone, methyldopa, penicillins, probenecid, procainamide, quinine, quinidine, ribavirin, rifampin, sulfonamides, & tetracycline. (**Direct antiglobulin test-DAT or Coomb's test** is used to detect cause of hemolytic anemia)	Direct DNA inhibitors– allopurinol, azathioprine, chemo meds, hydroxyurea, leflunomide, mycophenolate & zidovudine. Folate antagonists- carbamazepine, methotrexate, pentamidine, phenobarbital, phenytoin fosphenytoin, primidone, trimethoprim & valproic acid. Reduced folate or vitamin B12 absorption- alcohol, aminosalicylic acid, colchicine, cotrimoxazole, H2 blockers, isoniazid, metformin, neomycin, nitrofurantoin, oral contraceptives, proton pump inhibitors, sulfasalazine, tetracyclines & triamterene.

New FDA:

Ferric pyrophosphate citrate Triferic for iron replacement with CKD & on dialysis (27.2mg of iron may be added directly to hemodialysis solution in adults); SE: HA, edema, UTI, hypersensitivity rxn.

Ferric citrate **Auryxia** 1g 210mg ferric iron tabs, 2-4 tabs TID cc, ↓phosphate in pts on dialysis; AE: N/V/D, fecal discoloration, concern iron overload; DI: alendronate,ciprofloxacin,doxycycline,levothyroxine,Vit D. May ↑iron & ↓ESA in ESRD.

Ferric maltol **Accrufer** oral for iron deficiency in adults, 30 mg twice daily, taken 1 hour before or 2 hours after a meal.

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.

Adult CKD-Anemia Management Guidelines - Summary of Recommendations						
	KDIGO 2012[291] (International group)	**CSN (CAN) 2008 Guideline[292] + 2013 Commentary[293]**	**KDOQI (US) 2006 Guideline[300] (2007 Hgb update[301]) + 2013 Commentary[294]**	**ERBP (EUR) (EBPG 2004 Guideline[295]) + 2009 & 2013 Position Statements[296.297]**	**NICE (UK) 2015 Guideline[298]**	**Renal Association (UK) 2020[update] Guideline[299]**
General comments	Anemia simply defined as Hgb <130 male, <120 female. Move away from targets, use lowest effective ESA dose to prevent transfusion. Of the recommendations, two (5.4%) had high-quality evidence, & 9 (24.3%) had mod-quality evidence.	No evidence for treating ND-CKD with iron if Hgb >110 & not on ESA. Start ESA if iron corrected in ND-CKD and Hgb <100.[opinion] Noted evidence did not permit establishment of an upper limit for TSAT/ferritin.	Limited to ESA FDA black box warnings. Acknowledged uncertainty around long-term iron effects, however felt KDIGO overly cautious.	Anemia is defined as Hgb <135 male, 132 men[>70yo], <120 female in European popl'n. Allowed for higher Hgb targets in lower risk individuals.	Emphasize using lowest effective ESA dose to control anemia symptoms.	Investigate for anemia cause & treatment if Hgb <110 or symptomatic. Unknown if value in treating Hgb >120 if iron deficiency. Do not start ESA if ferritin <100 until corrected. Start ESA if likely to benefit in terms of QOL & function.
When to start/give iron (TSAT %, ferritin ug/L)	When TSAT ≤ 30 & ferritin ≤ 500; {decision to continue past these parameters based on patient response, Hgb conc, ESA dose [in ESA-treated], ongoing blood loss, trends in Hgb/TSAT/ferritin, and clinical status – though little evidence of benefit in treating beyond these TSAT & ferritin numbers}	Treat with iron when TSAT <20 & ferritin <100 (anemic ND/PD-CKD) or <200 (HD-CKD).	Treat with iron to keep TSAT >20, ferritin >100 for ND-CKD (if TSAT <30, could give iron even if ferritin >500), or ferritin >200 for HD-CKD (hold iron if ferritin >500).	Treat with iron when TSAT <20 (or if ↑Hgb wanted w/o ESA and TSAT is <25) Treat with iron when ferritin <100 (or if ↑Hgb wanted w/o ESA and it is <200 for ND-CKD or <300 for HD-CKD). Limit to TSAT 30 & ferritin 500.	Treat with iron to keep TSAT >20, and ferritin >100. Max ferritin 800 (review iron dose when ferritin >500).	Iron replete is TSAT >20% and ferritin >100. Do not exceed ferritin 800 for ND/PD-CKD (usual ferritin 100-500, r/a iron if >500). Do not exceed ferritin 700 (usual 200-500) for HD-CKD. In HD-CKD, give iron 400 mg IV qmos, unless ferritin >700 or TSAT ≥40.[1A, PIVOTAL]
When to start/give ESA & max Hgb (g/L)	Start ESA in HD/PD-CKD when Hgb 90-100 & consider in ND-CKD when Hgb <100. Generally, keep Hgb <115 (may ↑ to Hgb 115-130 if patient accepts risk trade-off for possible ↑ QOL). Strong evidence[1A] not to go above Hgb 130 with ESA.	Generally, start ESA when Hgb 90-100. (If hx stroke/cancer, initiate at Hgb ≤90 & target 90-105, with caution/avoid if active malignancy.) A range of Hgb 95-115 is acceptable, target 100-110. Do not support going >115 with ESA.	Keep Hgb <110	Keep Hgb ≤115 in most cases, do not exceed Hgb 130. Target Hgb 100-120, avoid >130[in young with few comorbidities]. In people with high risk, start ESA at Hgb 90-100, maintain Hgb ~100[caution if hx stroke or malignancy].	Target Hgb 100-120, adjust dose when Hgb <105 or >115.	Target Hgb 100-120 (mean 110).[2B] Adjust dose when Hgb <105 or >115.

CAN=Canadian **CSN**=Canadian Society of Nephrologists **EBPG**=European Best Practice guidelines **ERBP**=European Renal Best Practice EUR=European **KDIGO**=Kidney Disease Improving Global Outcomes **KDOQI**=Kidney Disease Outcomes Quality Initiative **NICE**=National Institute for Health and Care Excellence **UK-RA**=United Kingdom Renal Association **UK**=United Kingdom **US**=United States

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care professionals are also reminded that: Serious hypersensitivity reactions including life threatening and fatal anaphylaxis/anaphylactoid reactions have occurred in patients receiving intravenous iron products including FERAHEME®. FERAHEME® should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. Patients should be closely monitored for signs and symptoms of hypersensitivity, including clinically significant hypotension, during and for at least 30 minutes after each administration of FERAHEME®. Before each administration patients should be informed of the risk of hypersensitivity. Patients should also be informed of the relevant symptoms and asked to seek urgent medical attention if a reaction occurs.

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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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Patient Safety

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FDA Mar/10 In late April, Takeda Pharmaceuticals will begin marketing its proton pump inhibitor **Kapidex** (dexlansoprazole) under the new name **Dexilant**, owing to dispensing errors that have occurred from mix-ups with the prostate cancer drug Casodex (bicalutamide) and the analgesic Kadian (morphine).FDA news release
FDA May/18: Lake Michigan Distilling Company, LLC of La Porte, Indiana, doing business as **Ethanol Extraction, is recalling its 95% Ethyl Alcohol product ("Product") because of possible contamination with methanol**, a highly toxic type of alcohol that can cause serious and sometimes fatal damage if ingested by humans or animals. Recall of the Product was sparked by news that a man in Massachusetts allegedly ingested the Product and later died as a result. There have been no other reports of any ingestion or injury since the Product was first marketed in October 2016.
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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.}[45]
- **Approach for engagement**
  - Accept patient autonomy
  - Non-judgemental approach/Motivational Interviewing
  - Collaborative approach with patient
  - Confidentiality
  - Proactive discussion on meds and behaviours
- **Managing Potentially Violent Patient[46]:**
  - 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 [47,48]

- **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 [56]

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 or lorazepam for agitation & hypertension e.g cocaine induced - IV lorazepam, diazepam or midazolam short acting if severe agitation/anxiety - Optional (if predominant psychosis): sedating antipsychotic (e.g. olanzapine, risperidone, quetiapine) {Avoid mixing benzodiazepine & antipsychotic if possible due to risk of oversedation & respiratory AE - Monitor: hyperthermia, hypothermia, cardiac, electrolytes - HTN: benzodiazepines; alternatively nitroprusside, NTG - α-blockers. {generally avoid β-blockers as will result in unopposed α constriction} See also Stimulant Use Disorder Chart
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 [49]
- Other substances of abuse: volatile inhalants, Listerine mouthwash
- Be weary of illegitimate on-line pharmacies which supply controlled substances without a prescription.[50]

Acute Alcohol Intoxication[51,52]

- **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[53]:

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.}[54]

Substance Abuse in Older Adults[55]: 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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Extras Continued:

www.RxFiles.ca – Substance Abuse

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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Aboujaoude E. Psychology Today, Apr 2012: Accessed 09 May, 2012 http://www.psychologytoday.com/blog/compulsive-acts/201204/bath-salts.

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!"

Dimethoxybenzeneethanamine (2-CB) – (note 2-CB is a misnomer) a synthetic hallucinogen & club drug; sometimes sold as ecstasy; showed up in Prince Albert, SK, Feb 2017.

Poppers – volatile alkyl nitrite compounds inhaled for enhanced sexual experience. AE: foveal maculopathy (vision disturbance).

Kratom – herbal product, opioid agonist properties; mostly obtained as a powder and consumed as a beverage; doses >15g may produce opioid like toxicity; severe adverse events, including death, have been reported; naloxone may be given (if drowsy/respiratory depression).

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
- Vitamin C sometimes used as an acidifier to help dissolve substances (i.e. crack cocaine, heroin) for injection

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:

See RxFiles Alcohol Use Disorder Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Alcohol-Use-Disorder.pdf v

Pregnancy Screening: Alcohol, smoking, and other substance use in the perinatal period (BMJ)

Motivational Interviewing – Modules/videos exploring ambivoence in behaviour change: modules/videos of interest: https://www.youthaodtoolbox.org.au/motivational-interviewing

Get Help for Problematic Substance Use (Patient Links from Heatlh Canada): https://www.canada.ca/en/health-canada/services/substance-use/get-help/get-help-problematic-substance-use.html

Low Risk Cannabis Use Guidelines (for youth, by youth): http://www.camh.ca/en/health-info/guides-and-publications/lrcug-for-youth

SK Helath Links:

www.saskatchewan.ca/addictions; the target audience is the public.

Direct links re Crystal Meth:

- Infographic: http://publications.gov.sk.ca/documents/13/106826-Crystal-Meth-Infographic-2018.pdf
- FaQ : http://publications.gov.sk.ca/documents/13/106827-CM-FAQ-2018.pdf
- Fact Sheet : http://publications.gov.sk.ca/documents/13/99220-CrystalMeth%20Factsheet%20Sept%202016.pdf

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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.
Health Canada Jun/17 is advising health care professionals and Canadians that the **Canadian authorized version of NARCAN** will transition onto the market by July 5, 2017. NARCAN is a nasal spray form of naloxone, the life-saving drug that temporarily reverses the effects of an opioid overdose.
Health Canada June/18: Health Canada reminds Canadians of the **limitations of fentanyl test strips being used to check street drugs** before consumption.
Health Canada Sep/19 is advising Canadians about the increased risk of **opioid overdose and serious side effects when taking gabapentin (e.g., Neurontin) or pregabalin (e.g., Lyrica)** with an opioid.
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Refractory psychosis associated in patients with SUD and mental illness
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ADHD tx options in stimulant use disorder
- Patients with ADHD and SUD are at higher risk for diversion and misuse of stimulants. Non-stimulants such as atomoxetine may be considered/preferred.]
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Mirtazapine for methamphetamine use disorder in cisgender men and transgender women may benefit (resulted in reduced meth use and HIV risk behaviours).[48]

Meth treatment does not require stimulant specific groups
- Existing treatments are effective in reducing craving and psychiatric symptoms. Additional stimulant specific groups do not appear to influence treatment completion and secondary outcome measures. Institutions should therefore offer treatment for methamphetamine users, even if they do not provide a therapy content focusing on methamphetamine. History of injection drug use should receive attention in treatment to prevent drop-out. Changes in cognitive functioning need to be further explored.
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Fatal Overdose Risk
- Stimulants (+/- opioids) were involved with >45% of the overdose risks in one USA analysis for2019.[55] Approximately 50% of stimulant cases represented by crystal meth. Implications: look for the overlap and increased risk of co-use of stimulants and opioids.

Heart Risk - Cocaine
- Usual risk scoring (e.g. HEART Risk Score) in in cocaine users presenting to Emerg is not adequate to detect true risk of MACE. Need increased suspicion of CV risk.

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6) Adopting a Continuum of Care Approach for Substance Use Disorders[12]

CONTINUUM OF CARE	HARM REDUCTION	
	Screening	Identify those who may be at risk
	Assessment	Diagnose, assess severity, & intensity of tx needs
	Brief Interventions *Ask, Assist, Advise*	Provide harms info; explore motivation to change
	Special Access Clinics	Option of specialist involvement when needed
	Community Outreach	Education, harm reduction resources, referrals, outreach programs
	Withdrawal Management	Interim pharmacological & psychological supports
	Pharmacological Interventions	Sometimes an option to help achieve desired outcomes in SUD
	Psychosocial Interventions	CBT, contingency management, counselling
	Recovery, Sustaining Wellness & Ongoing Care	Ongoing supports, formal & informal, to help change lifestyle & behaviour

A SUD is a chronic disease. Patients with a SUD will require acute & ongoing intervention. A continuum of care approach supports patients in accessing various levels & intensities of care over time. An effective team approach is often the critical factor toward a successful outcome.

Best Practices (Adapted) [13]
1) Individual experiencing harm should determine ultimate goal of treatment (e.g. safer use, abstinence, etc.) with input from provider
2) Determine treatment plan together and offer stepped care with least intensive services first
3) Assess, address, coordinate all wellbeing components
4) Ensure services are culturally, trauma & gender informed
5) Reduce stigma to overcome major recovery barriers
6) Peer-engaged and peer-led services help with trust
7) Enhance outcomes by being recovery-oriented

Harm Reduction Measures
1) Address risks for other diseases (e.g. HIV, Hep C, syphilis)[14]
a) screening, b) needle distribution & exchange programs,
c) vaccinations, d) counselling regarding risky behaviours,
e) safer smoking options, f) referral to related services
2) Educate regarding responding to overdose, (including recommending take-home naloxone)
3) Inform re supervised consumption services when available

A non-judgemental attitude is a key for success!

Psychostimulant	220

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Pharmacological Options for AUD & other comorbidities

Comorbidities	Consider…	Comments
Adherence issues	Naltrexone (once daily dosing)	Acamprosate (TID dosing) = not convenient
Abstinence vs Craving	Acamprosate is most effective for abstinence maintenance & ideally initiated within 4-7 days after detox.	Naltrexone is most effective for craving management & can be given while drinking and/or as needed when cravings occur.
Bipolar	Topiramate	Antidepressants may worsen mania.
Depression, Anxiety	Sertraline & Naltrexone combination	SSRIs (e.g. fluoxetine), SNRIs (e.g. venlafaxine), or mirtazapine if sertraline previous tried/failed.
Insomnia	Acamprosate, gabapentin, topiramate	If depressed, may also consider mirtazapine
Lactation	Naltrexone appears to be minimally transferred into breast milk.	Abstinence preferred. Limited data for acamprosate or naltrexone. Disulfiram is contraindicated.
Liver failure, acute hepatitis	Acamprosate, disulfiram, topiramate	Naltrexone is contraindicated in hepatic disease (e.g. LFTs≥3x ULN and abnormal bilirubin).
On opioid (e.g. codeine, oxycodone)	Acamprosate, disulfiram, topiramate	Naltrexone is contraindicated. Patient should be opioid free for 7-10 days before given naltrexone to reduce risk of severe opioid withdrawal symptoms.
Pregnancy	Naltrexone? Lack human studies.	Abstinence preferred. Safety of acamprosate, disulfiram & naltrexone in pregnancy unknown.
Psychosis	Benzodiazepines (BZDs) for acute alcohol withdrawal	Caution long-term use of BZD (abuse potential, adverse effects, relapse, opioid overdose deaths reported with benzodiazepines, binge drinking and opioid combination)
Renal impairment	Naltrexone, disulfiram, topiramate, ↓acamprosate dose.	Acamprosate is contraindicated in severe renal impairment (CrCl≤30mL/min)

Diazepam vs. Lorazepam for alcohol withdrawal

- Benzodiazepines are used to suppress withdrawal symptoms with minimal sedation
- No systematic review has conclusively established that one class of benzodiazepines is superior to another for alcohol withdrawal management.[BC AUD guideline 2019]
- Benzodiazepines are generally not a preferred option for outpatient withdrawal management due to their AEs (e.g. respiratory depression with alcohol), tendency to potentiate the effects of alcohol if used concurrently, and potential for non-medical use/dependence. Although not preferred, if benzodiazepines are prescribed for outpatient withdrawal management, prescribe short course prescription with a fixed-dose schedule, daily dispensing from pharmacy, & frequent clinic visits. [BC AUD guideline 2019]
- Diazepam or lorazepam: use when CIWA-Ar score ≥ 10 after patient has stopped alcohol for 6-12 hours after the last drink.

	Diazepam	Lorazepam
Advantages	Diazepam is 1st line. Diazepam is a longer-acting benzodiazepine that may be more effective in preventing complications such as seizures.	Lorazepam is preferred if the patient is 60 or older, hepatic dysfunction, low serum albumin, or on opioids or other sedating medications.
Disadvantages	Diazepam and the active metabolites are renally excreted and can accumulate in the elderly. Diazepam is metabolized in the liver & may accumulate in liver dysfunction.	Lorazepam has a shorter half-life.
Office protocol	Advise patient to have their last drink the night before morning appt. CIWA-Ar score ≥10: 20 mg Q1-2H PO until symptoms resolve and CIWA-Ar score <8 on 2 consecutive readings, at least 1 h apart. If CIWA-Ar score increases and/or does not improve after 4 doses, refer to ED.	Advise patient to have their last drink the night before morning appt. CIWA-Ar score≥10: 1–2 mg Q2–4H PO or SL until symptoms resolve and CIWA-Ar score <8 on 2 consecutive readings, at least 1 h apart. If CIWA-Ar score increases and/or does not improve after 4 doses, refer to ED.
Home protocol	• The patient has the last drink between 6:00 and 8:00 p.m. the night before. • The patient takes 10 mg of diazepam, dispensed by the support person, starting the next morning, every four hours as needed for tremor. • Prescribe no more than 40 mg of diazepam. • Reassess the patient the next day (by phone or in person). • The patient visits the clinic within two to three days.	No regimen available or provided by CAMH or BC substance abuse

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References – RxFiles - Alcohol Use Disorder (AUD) Tx Chart

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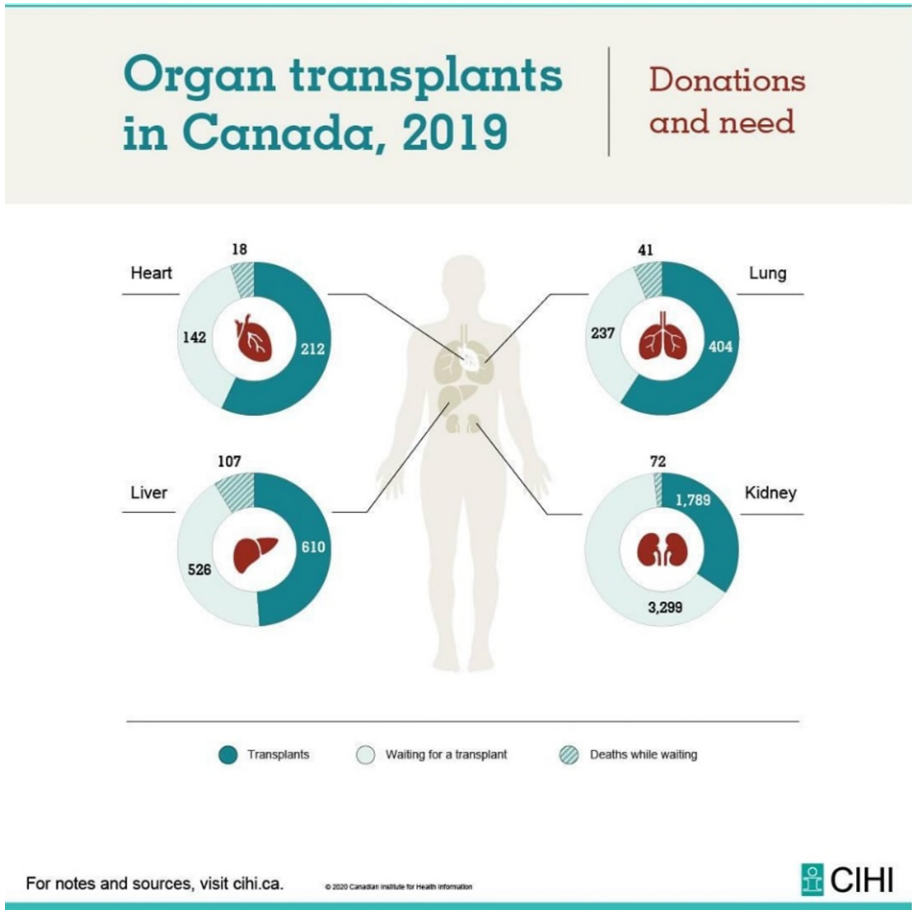

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Organ Transplant Facts:

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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