RxFiles Potpourri of Q&As
Osteoporosis, Vitamin D, SMBG & Anti-infectives

Oct 2010

OSTEOPOROSIS (OP)

Should consideration be given to a "drug holiday" for patients on a bisphosphonate?

- Recent concerns about long-term treatment have raised the proposition of whether a "drug holiday" should be considered for bisphosphonate patients.[1,2,3] (See SDIS Bisphosphonate Safety[4] & the RxFiles OP Treatment Chart[5] pg 72-73
- Rather than consider a drug holiday, one should consider the patient's overall fracture risk and whether a bisphosphonate is actually indicated.
  - For patients with high fracture risk, benefit is generally considered to outweigh the possible risks of long term therapy which are **rare** (e.g. osteonecrosis of the jaw[6], atypical fractures[7], atrial fibrillation[8] and esophageal cancer[9]).
  - For patients with low fracture risk, discontinuation of bisphosphonate therapy should be considered.
  - Some low/moderate risk patients may be unnecessarily receiving bisphosphonates due to the shift in guidelines to consider overall fracture risk[10,11] rather than just bone mineral density (BMD).[12]
- Tools are available to estimate overall fracture risk:
  - BMD lab reports that include a 10 year fracture risk
  - Graphical estimate (data strongest for women)[13]
  - FRAX risk assessment (Canadian Data Set - available)[14]
- Special consideration should be given to higher risk if:
  - **fragility fracture** history after age 40
  - **corticosteroid** use (>3 months with ≥2.5mg prednisone/day)
  - **smoking**
  - **family history** of osteoporotic fracture, especially hip

How can we improve adherence to bisphoshonates therapy when indicated in high risk patients?

- A Quebec cohort study found that 52% of women over age 70 years had discontinued therapy after 12 months.[15]
- To increase adherence consider the following:
  - cost issues (see table 1)
  - less frequent dosing. {Weekly regimens may be associated with less discontinuation than daily.[16]}

Table 1: Bisphosphonate – OP Regimens & Cost/Year

Alendronate generic	10mg po daily in am	$520
Alendronate generic	70mg po once weekly	$400
Alendronate FOSAMAX	70mg po once weekly	$710
Alendronate/Cholecalciferol FOSAVANCE In Sask. only need OP diagnosis for EDS coverage.	70mg/5600 IU po weekly	$360
Risedronate generic	35mg po once weekly	$360
Risedronate ACTONEL	150mg po monthly	$840
Zoledronic acid ACLASTA	5mg IV yearly	$740

Note: Etidronate DIDROCAL low cost ($160/year) but lacks hip fracture evidence.

What dose of Vitamin D is recommended in OP?

- There has been a lot of discussion about the prevalence of Vitamin D deficiency and claims for benefit of supplementation.
- There is evidence for the safety and efficacy of daily maintenance doses in the range of 800-2,000 IUs (international units) of vitamin D in those age >50.[17] Specific dose recommendations will vary depending on age, season, etc. (See Vitamin D Claims - Q&A [18])
- An initial loading dose is sometimes used if serum 25-OHD levels are less than 25-50 nmol/L. {Generally, only recommend **levels** if there is a high risk of deficiency or toxicity concern.} Not routinely: 17,19

What is the status of calcium given the recent concern about a possible association with MI?

- A recent meta-analysis of randomized controlled trials (RCTs) found that persons taking calcium supplements without vitamin D had an increased risk of MI.[20] The meta-analysis had limitations which have been discussed elsewhere.[21] {Based on patient level data, from 5 studies of over 8,000 patients, the number needed to harm (NNH) was 69; e.g. for every 69 patients treated with calcium 500mg or more for 5 years (without vitamin D), there was one extra MI.}
- Current take home messages for most patients:
  - Avoid exceeding the maximum daily 1.5g/day intake for combined pills and diet (1,200mg elemental calcium for menopausal women and men >50yrs)
  - Since patients typically get 300-800mg or more in their diet, this means that a supplement providing 500 – 1000mg of elemental calcium is enough for most, and some may not require any.
    ⇨ See Calcium Calculator tool(s) online [22,23]
  - Ensure adequate vitamin D intake and avoid excess calcium!

Highlights

1) When deciding whether to treat osteoporosis (OP), **assess fracture risk** rather than BMD alone.
2) The benefit of bisphosphonates is generally considered to outweigh harms in OP patients who are truly "high risk". However, patients at low-moderate risk of fracture may be receiving bisphosphonates unnecessarily, and the safety concerns may outweigh any benefit.
3) Ensure adequate vitamin D (e.g. 800 – 2,000 IU) for most OP patients, but avoid excessive calcium!

Bone care/hygiene for all: ↓ falls/alcohol/smoking, ↑ exercise.

Self Monitoring of Blood Glucose (SMBG)

How useful is SMBG for non-insulin patients with T2DM?

- The value of routine ongoing SMBG, especially in most patients not on insulin, has come into **question**, due to uncertain or marginal benefits & significant cost.[24,25,26,27,28,29,30,31,32] A possible association with depression[33] & lower quality of life[34] has been noted.
- When considering whether to & how often to test, ask, "Will the test result in a positive behaviour change?"[35]
- For more information, see RxFiles SMBG Chart[36] pg 26 and the comparison of COMPUS and CDA recommendations relating to SMBG.[37] [It is estimated that > $150million/year could be **saved** with more targeted SMBG without adversely affecting health outcomes.[38 Canada]]

Influenza Immunization Update – Fall 2010

- The Fall 2010 vaccine will cover three strains:
  - A/California/07/2009 (H1N1); pandemic strain from 2009
  - A/Perth/16/2009 (H3N2)
  - B/Brisbane/60/2008
- Vaccine will be non-adjuvanted.
- Vaccine is recommended for everyone age ≥6months without contraindications. (Coverage will again be universal in SK.)
- Efforts should ensure that those at higher risk are especially encouraged to get the vaccine.

{Healthy kids 6months - ≤4yr (give 2 vaccine doses 4 wks apart for kids <9yrs who were previously unvaccinated [previous H1N1 not count]); People providing regular care to young kids [<2-4yr], kids on ASA [long term]; if heart, renal, cancer, neuro, diabetes or lung dx; BMI ≥ 40, Aboriginals & in **elderly ≥65**; nursing home, & in pregnant ♀; also those capable of transmitting to high risk people such as health care workers.}

For more information , see RxFiles Influenza Chart.[39] Pg 60

New & Worrying – we wish it were not so… The NDM-1 Super-bugs

- This gene first appeared in New Delhi, India, and has now surfaced in Canada, the USA and Great Britain.[40]
- The gene has been sequenced in various bacteria (*E. coli, K. pneumonia*, and *Enterobacter cloacae*).
- Appears to be resistant to almost everything, except possibly colistin and tigecycline. Encourage hand hygiene, surveillance and isolation.

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Loren Regier (left) and Brent Jensen receive the award on behalf of RxFiles at the Family Medicine Review Dinner in Saskatoon.

Dr. Michael Krochak Award

recognizing significant contribution to the practice of family medicine

College of Family Physicians of Canada – Sask Branch.

24 September 2010

Thank you!

Anti-infectives for Common Infections - Select Chart Highlights (from page 54-55 of 8th Ed RxFiles book)

Viral Infections

- Remember the many infections for which the initial cause is predominantly viral:
  - Pharyngitis, especially in adults
  - Acute bronchitis [< 10days]
  - Acute sinusitis [< 10days]
- Antibiotics are often not necessary! If treating with antibiotics, consider an agent with a narrow but suitable spectrum; treat only for time indicated.

Acute Otitis Media (AOM)

- Watchful waiting has been recognized as a valuable strategy to reduce antibiotic overuse in some otherwise healthy children, >2yrs of age. {It may be appropriate for children 6 months to 2 years when appropriate medical follow-up [at 24hours] can be assured.}
  - Treat ear pain with adequate doses of acetaminophen or ibuprofen
  - If symptoms do not improve in 2-3 days:
    - Verify diagnosis as necessary
    - Start antibiotic treatment
      - X5 days in age >2yrs (including adults)
      - X10 days in age <2yrs
- Amoxicillin is still often the drug of choice, but **high dose** (~ 80mg/kg/day) is often recommended in AOM to cover intermediate resistant *Streptococcus pneumonia*. {To achieve high dose amoxicillin with amoxicillin/clavulinic acid, may give amoxicillin 40mg/kg in addition to amox/clav 40mg/kg per day.}
- Amoxicillin may be given q12h (usual max **3**-4g/day); these doses are relatively high even by adult standards. [See: RxFiles Anti-infective Common Infections Chart[41] pg 54-55]

Cephalexin (Keflex): when and when not to use

- Cephalexin is useful for **skin infections** caused by methicillin sensitive S. aureus or streptococci.
- It should not commonly be used for **respiratory** infections as it does not cover usual pathogens. Limiting use will help preserve effectiveness for skin infections.

Deferred prescriptions

- A deferred prescription (e.g. provisional "wait and see") may be useful in some cases, where patient can be instructed to fill "only if…".

Trends in Anti-infective Therapy

- Macrolide resistance has been increasing (Penicillin Resistant Strep Pneumococcus: ~20% are macrolide resistant)
- To minimize antibiotic pressure and emerging resistance, ensure adequate dose for shortest effective period of time. (Hit hard & short!)

Lots more in the chart (Pages 54-55 in the **RxFiles Comparison Charts - 8th Edition book**), or check out the **Anti-infective Guidelines for Community-acquired Infections – 2010 (orange book)** available from MUMS Guidelines.
Tel: 416-597-6867; Toll Free: 1-877-876-4580, or
Email: guidelines@mumshealth.com; Web: www.mumshealth.com

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Osteoporosis (OP) Treatment Comparison Chart [1,2 CDN OP'10, SOGC'09, 3, 4, 5 NAMS'10] www.RxFiles.ca

M. Jin, PharmD, B. Jensen BSP Oct 10

Treat **High Absolute 10yr Fracture Risk, & Spine or Hip #** pts, NOT low or moderate # risk pt unless exceptional circumstances. Take age, sex, steroid use, family history, smoking & fragility # [after age 40]; not just BMD, into account.

	Generic/TRADE Strength & forms, g=generic avail.	Side Effects (SE) / Contraindications CI NNT's may mislead; most OP trials had mix of low, moderate & high # risk pts.	Hip #	Vertebral #	√ = therapeutic use / ×= Disadvantage / Comments / Drug Interactions DI / Monitor M	USUAL DOSE	$/year g=generic
BISPHOSPHONATES antiresorptive	**Alendronate, risedronate or zoledronic** [acid] ↓ vertebral # [↓RR~ 50%], nonvertebral & hip # [↓RR ~30%] in **HIGH** risk OP pts; & FDA approved for OP in **MEN** & **GIO**. [Glucocorticoid Induced Osteoporosis 2] (may ↓skeletal complications/pain in multiple myeloma, [breast, lung & prostate cancer pts]) **Mechanism**: Anti-resorptive which binds to hydroxyapatite, inhibits the osteoclast, which decreases the resorption & turnover of bone, which increases BMD [often a 2-6% increase in BMD over 1-3yr]. Limited oral bioavailability (<1%). **M**: # risk, height, iliocostal distance; BMD in 1-3yr. Fall hx [6,7,8] Reassess existing pts [Consider Indefinite **Drug Holiday** (?1-3-5yr) after 5yr [9 FLEX,10, 11]] of continuous tx only **if** not now or perhaps never were at high # risk. (effects **persist** since meds in bones for **yrs**). **Caution**: bisphosphonate in **Stage 4-5 CKD** (1st rule out adynamic bone dx usually by lab +/- biopsy findings) or in **transplant** pts if only high OP risk but not #'s. **Ensure Bone Care/Hygiene**: lifestyle [exercise-wt bearing], Vit D, Ca++, ↓falls/alcohol/smoking **Possible long term Tx concerns**: 1) osteonecrosis of jaw (**ONJ**) [avascular necrosis]: rarely occurs; if cancer, extensive dental procedures & **high dose/long term IV** bisphosphonate used [very rarely on oral tx, >1 in 100,000 pt yr]; may benefit postponing tx until **invasive** dental work done. Dental exam with X-ray in high risk pts. Use good oral hygiene & report dental concerns. (Consider holding bisphos [for invasive dental procedure: if on bisphos tx for >3yr, esp. if on steroids. If hold tx: stop 3month before; & until ~3months after dental procedure. Lacks evidence AAOMS'09)] [12,13,14] 2) **Atypical sub-trochanteric #** [very rare long term 15] mid-shaft # eg. femur spike or beak configuration & cortical thickening at # site; ?↑ microcracks may present as **thigh pain** or hypersensitivity [reaction]. 3) **Atrial fibrillation** [rare]: reports with IV zoledronic [acid 16] 4) **esophageal cancer?** [17] **Others** [not official OP indication]: **Pamidronate** Aredia 30,60,90mg IV; 30mg IV 2hr D5W q3mon $450/yr, approved: Paget's dx & Hypercalcemia [of Malignancy]. **Clodronate** Bonefos 400mg cap; 300mg/5ml amp IV, approved: Hypercalcemia & osteolysis.					
	Alendronate, ☎ ✆ **Fosamax** ,g (5 X), 10, 40 [Paget's] & 70mg tabs 70mg/75mL oral soln {raspberry flavour} ⊗ (each pack = 4 bottles of 75mL) --- **Alendronate/cholecalciferol** tabs **Fosavance** 70mg/70ug (2800IU Vit D_3),X ✆ 70mg/140ug (5600IU Vit D_3) ☎[OP] ✆ (Nitrogen containing⇒potent)	**Common: GI SE**: (abd pain ~7%, acid regurgitation ~2%, constipation ~3%, diarrhea 3%, dyspepsia ~4%, flatulence ~3%, nausea ~4%), headache ~2%, taste [distortion] ~1% **Serious**: Esophagitis, esophageal ulcers 1.5%, erosions, stricture, perforation; gastric ulcer 1%; bone, joint ± muscle pain ~4%, muscle cramp ~1%, ocular disorders, ONJ [rare] **CI**: **esophagus** abnormalities: Barrett's, delayed esophageal emptying [stricture, achalasia]; inability to stand/ sit up ≥30min; hypocalcemia; pregnancy & nursing moms; & renal dysfx: CrCl **<35** mL/min [weigh risk vs benefit if stable CrCl & definite OP]	NNT = 91 for 3 yrs [1.1 vs 2.2%] in ♀ with previous vertebral# [18 FIT] NS: **Primary** prevention Cochrane 19	NNT = 37 for 3 yrs [2.3 vs 5%] in ♀ with previous vertebral# [20 FIT] Cochrane: [19 ~3yr] 1[0] prev: NNT=**50** 2[0] prev: NNT=**17**	**DI**: ↓ absorption [alendronate]: Calcium, antacids, iron, food/beverages [water ok] Impair cholecalciferol absorption: bile acid sequestrants (eg. cholestyramine, colestipol), mineral oils, olestra & orlistat. ↑cholecalciferol catabolism: anticonvulsants, cimetidine, thiazide [but ↑ ca++] **Men**: data only from secondary trial analysis. **Elderly**: studied up to age 91 Take at least **30 min before** first food/drink/medication of the day with a full glass of water (**240mL**); do not lie down for 30 minutes after. Low cost, very good fracture outcome evidence & 10yrs of data. [Approved 1995]	10mg OD in am 70mg once **weekly** 70mg soln once **wkly** --- 70mg/[2800IU] once **wkly** 70mg/[5600IU] once **wkly**	520 g 400 g (710 [Trade]) 710 --- 340 X ✆ **360**
	Risedronate ☎ ✆ **Actonel**, g 5, 30, 35, (75 [D/C],150mg ⊗) tabs **Actonel Plus Calcium** X ⊗ -D/C soon 4 Risedronate 35mg tabs & 24 calcium 1250mg tabs {500mg elemental calcium} – 28d supply (Nitrogen containing⇒potent)	**Common**: **GI SE**: (abd pain ~4%, diarrhea ~3%, dyspepsia ~5%, flatulence 2%, gastritis 1%, vomiting~1%), asthenia 1%, headache ~3%, pruritus 1%, rash 1.4%. **Serious**: arthralgia ~2%, myalgia ~1%, gastritis erosive ~1%, iritis [rare], uveitis [rare], ONJ [rare] **CI**: Hypocalcemia, pregnancy & nursing moms; **esophagus** abnormalities: Barrett's, delayed emptying [stricture, achalasia], renal dysfx: CrCl **<30** mL/min [weigh risk vs benefit if stable CrCl & definite OP]	NNT=91 for 3 yr in ♀ with or without prev vertebral# [21 HIP] NS: **Primary** prevention Cochrane 22	NNT=15 or 20/ 3yr in ♀ without prev vert. # [23] or with # [24 VERT] NS: **Primary** prevention Cochrane 22	**DI**: ↓ absorption [risedronate]: Food, antacids/supplements which contain polyvalent cations (e.g., calcium, magnesium, aluminum & iron). **Men**: data only from open label trials. Take at least **30 min before** first food, beverage, or medication of the day with water (**≥120mL**); do not lie down for 30 minutes after. **Elderly**: a few trials studied people over 100yrs. Convenient monthly dosing with possibly less GI SE & 8yrs of data.	5mg OD in am 35mg once weekly 150mg tab q **month** 150mg [75mg x2] q **mon** (75mg soon D/C)	870, [445 g] ⊗ 710, [360 g] ⊗ 840 ⊗ **690**
	Zoledronic acid **Aclasta** ☎ ✆ **5mg/100mL IV** infusion, (Paget's), (Nitrogen containing⇒potent) **Zometa** X ⊗ (Osteolytic lesions of multiple myeloma, Hypercalcemia of Malignancy) **4**mg vial (give as 100mL **IV** infusion) For My Bones: 1-877-580-5338 Novartis program: gives IV clinic locations & helps to arrange monthly payment plan options.	**Common**: **Post-dose Sx**: fever [18%], myalgia [9%], headache [6%], flu-like [8%], arthralgia [7%], {mild-mod. in nature & resolve ~3day; some ≤7-14day ↓ in 2nd injection: acetaminophen/ibuprofen [may help]} **Hypocalcemia** (usually asymptomatic, but Sx: numbness or tingling sensation, esp. near mouth, muscle cramp/spasm); redness, swelling &/or infusion site pain; eyes [pain, redness, itching]. **Serious**: ?↑Atrial fib [serious: 1.3 vs. 0.5% placebo], ONJ [rare], acute **renal** failure [may ↑with quick infusion rate; rare], musculoskeletal pain [rare], bronchoconstriction in **Aspirin**-sensitive pts. **CI**: Pregnancy, nursing moms, non-corrected hypocalcemia, renal dysfx: CrCl **<30** mL/min [weigh risk vs benefit if stable CrCl & definite OP]	NNT = 91 for 3 yrs in ♀ with or without a vertebral # [25] HORIZON	NNT = 13 for 3 yrs in ♀ with and without a previous vertebral # [26] HORIZON	Zoledronic [acid] is a potent antiresorptive, has ↓GI SE, & given IV q1-2yr **DI**: Aminoglycosides (↓ serum calcium level), loop diuretics (↑ risk of hypocalcemia), nephrotoxic drugs such as NSAIDS **Hydrate** prior to admin: drink ≥2 glasses of fluids/water before & after. Post recurrent hip # trial [Horizon]: ↓ **mortality** [13.3 vs 9.6%], NNT=27 [over 1.9yr] [26] **Men**: 24% of pts in RCT [12] were men, but sub-analysis not published **M**: Serum calcium, vitamin D, renal function (Scr, eGFR) before every tx. Acetaminophen or ibuprofen may ↓ incidence of post-dose Sx's. ☎ Criteria–symptomatic tx of **Paget's** disease of the bone (one tx/yr) Least GI SE, infrequent q1-2yr IV infusion, but limited drug plan coverage.	Treat: 5mg IV infused over NO LESS than 15 minutes once/**yr**; Prevent: 5mg IV infused over NO LESS than 15 min every 2yrs; RCT trials out to 3yr.	**740** 365 X ⊗ for OP
	Etidronate (Eti) **Didronel**, g 200mg tab **Didrocal kit**, g 14 x Etidronate 400mg [white] PLUS 76 Calcium Carbonate [blue]1250mg (500mg elemental Ca^{2+})	**Common** [vs pl]: **GI SE**: (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^{++}, pregnancy/lactation	NS compared to calcium ± vitamin D placebo [27] Cochrane	NNT = 20 for 3 yrs in ♀ who had a previous vertebral # [27] Cochrane	Etidronate is a **weak antiresorptive** agent & may be effective in ↓risk of vertebral # in those at high risk.[2] (not ↓ hip or non-vertebral #'s) **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. Lowest cost, but less fracture outcome evidence.	Eti 400mg hs x 14 d, then calcium 500mg daily x 76days ⇒ cycle therapy. {**Continuous** eti can impair mineralization of the bone}	**160** g, (230 [Trade]) {Full formulary} SPDP&NIHB
SERM	**Raloxifene** ☎ ✆ **Evista**, g 60mg tab -antiresorptive	**Common** [vs pl]: Vasodilatation [flushing 10 vs 6%], flu like [14 vs 11%], leg **cramps** [7 vs 4%], ?↑diabetes mellitus [1.2 vs 0.5%] **Serious**: **VTE** [3.32/1000 ♀ yrs vs. 1.44 placebo (**OR**: 1.9 for PE, 1.5 for DVT)] **CI**: ♀ of childbearing potential [risk fo congenital defects in fetus], ♀ with active/past venous thromboembolic events (DVT, PE, retinal vein thrombosis) ↑ fatal **stroke** [0.22 vs 0.15% RUTH 28]	NS compared to placebo arm	NNT = 29 for 3yr in ♀ with & without a previous vertebral#[29 MORE]	Raloxifene ↓'s the risk of **vertebral #** [2, MORE, but not non-vertebral or hip #] Benefit pts with **breast cancer** risk. [30 STAR] (Lipid: may ↑HDL-C, ↓ total cholesterol & LDL) If **pt >65yr** & on raloxifene, consider switch to alternate agent. [b/c stroke & VTE risk] **DI**: Cholestyramine ↓ [raloxifene effect], warfarin ↓INR **M**: VTE Limited role: weigh stroke/VTE risk against modest breast ca & OP outcomes.	60mg PO OD	**630** g, (870 [Trade])
	Calcitonin Salmon ☎ ✆ -antiresorptive **Miacalcin**, g 200IU/**nasal spray**, 14 doses/bottle {1 pack=2 bottles} Unopened, store in fridge (2-8°C); after priming store at room temp (15-30 C) & use within 4 wks {SC inj 100[iu/ml Caltine],400[iu/4ml Calcimar]} ☎ ✆	**Common** [vs pl]: Rhinitis [8 vs 5%], nasal dryness [4 vs 3.6%], epistaxis [2.4 vs 2%], nasal discomfort [1.6 vs 1%], sinusitis [1.6 vs 0.5%], abd pain [3 vs 1.5%], nausea [1.7 vs 1%], dyspepsia [1.6 vs 0.3%], fatigue [1 vs 0.3%], hypertension [1.7 vs 0.8%], dizziness [1.6 vs 0.8%]. **Serious** [vs pl]: back pain [3 vs 0.8%], rhinitis ulcerative [3.4 vs 1.6%], cataract [3 vs 1.3%]	NS compared to placebo arm	NNT = 12 for 5 yrs in ♀ who had a previous vertebral # [31] PROOF **Trial Limitations**	Calcitonin considered to ↓ the risk of vertebral #s. [but not non-vertebral or hip # 2] **Weak antiresorptive** agent (consider use in ♀ >5yrs PM, unless for pain) **√Useful for pain from acute vertebral compression #s** [esp. first **1-3 months**] **DI**: Lithium ↓[lithium concentration].	1 spray = 200IU/d, intranasally, alternating nostrils daily Upon first use only, must prime pump.	**720** g

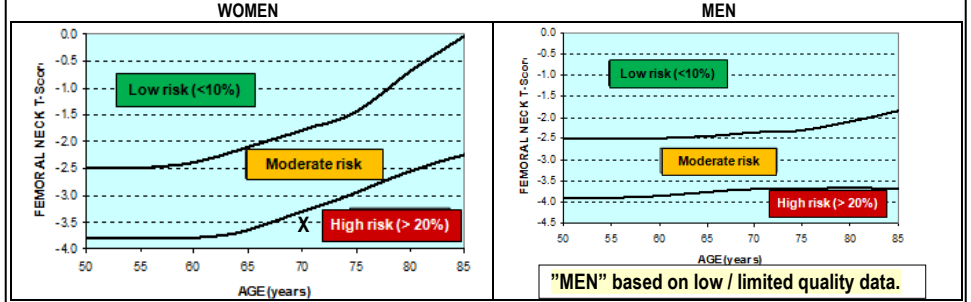
	Generic/TRADE **Strength & forms,** g=generic avail.	Side Effects (SE) / Contraindications CI NNT's may mislead; most OP trials had mix of low, moderate & high # risk pts.	Hip #	Vertebral #	√ = therapeutic use / ×= Disadvantage / Comments / Drug Interactions DI / Monitor M	USUAL DOSE	$/year g=generic
PTH	**Teriparatide** *X*, ⊗ **Forteo** (1-34 PTH) 750ug/3mL prefilled pen syringe - **anabolic**: ↑ osteoblast activity {PTH I-84 PreOs} avail in Europe Forteo Customer Care Program: 1-877-436-7836 Possible financial assistance by Eli Lilly.	**Common** vs pl: Nausea 9vs7%, dizzy 8vs5%, cramp leg 3vs1%, syncope 3vs1% **Serious** vs placebo: Osteosarcoma rats, **hypercalcemia** symptomatic (eg. nausea, vomiting, constipation, lethargy, muscle weakness), hyperuricemia 3 vs 0.7%, angina pectoris 3vs2%, arthralgia 10vs8%, tooth disorder 2vs1% **CI**: Pre-existing hypercalcemia, severe renal impairment, metabolic bone dx other than primary OP (incl. Paget's dx, hyperparathyroidism), unexplained ↑ alkaline phosphatase, prior skeleton external beam or implant radiation tx, bone metastases or skeletal malignancies hx, pregnancy, nursing moms, kids or young adults with open epiphysis.	NS compared to placebo arm [32]	NNT = 11 for 1.5 yrs in ♀ who had a previous vertebral # [32]. May ↓ pain from vertebral #..	Teriparatide considered to ↓risk of vertebral & non-vertebral #s, not hip #'s in postmenopausal ♀ with very **severe** OP. [2] √Recommend if ⇒ prior fragility # + {very low BMD (below -3 to -3.5), pts who continue to #, or lose BMD despite taking antiresorptive tx's}. Osteoporosis in **MEN**: approved for tx some evidence for benefit, no # data available. Glucocorticoid Induced Osteoporosis **GIO**: approved for tx If start PTH, D/C bisphosphonate usually; then when D/C PTH, restart bisphosphonate. **DI**: Digoxin ↑Dig level? {May help bone of oral cavity} Bashutski'10	20ug SC qd, up to 18 months 2yr FDA Refrigerate, discard pen after 28 days	**9000**
Ca & Vit D	**Calcium**, g *X* ▼ Oral, chew, dissolvable tablet; liquid NIHB covers ▼: Calcium 500mg, Calcium 500 + Vit D 125IU, & Calcium 500 + Vit D 400IU Pt with chronic renal failure, NIHB ▼: Sandoz, Gramcal, Calsan, Os-cal 250mg, Calcium Ca^{++} content: carbonate 40%, citrate 21%	**Common:** Constipation, bloating **Serious:** Renal stone {HR = 1.17, 95% CI, 1.02 to 1.34} [33] WHI, but uncertainty because no correlation with total daily calcium intake & kidney stone formation. Adverse effect of total calcium intake in excess of >2g/d may include high blood calcium levels, renal function & renal calculi formation WHI. (?? ↑ MI Bolland'10 7 trials HR=1.27, 95% CI= 1.01-1.59) {No recorded cases of calcium intoxication from food.}	Ca+Vit D: RR=0.84, 95% CI 0.73-0.96 [34] Cochrane NNT=45 for 2-5 yrs in ♀ with or without a previous vertebral # [35] Meta-analysis High 500,000 IU/yr⇒↑#'s Sanders'10	NS [34]	Calcium & Vit D supplementation alone insufficient to prevent # in those with OP; but critical **adjunct** with antiresorptive & anabolic OP meds [2] Consuming ≤500mg calcium elemental at one time maximizes absorption. [5] Include diet & supplemental calcium in daily intake needs. {**Dietary** calcium content: ~**300mg** in each⇒ a normal diet; 1 cup milk; 1 cup orange juice calcium fortified; ¾ cup yogurt; & cheese ~½ pack of cards sized serving} Take calcium with a **meal**: ↑bioavailability calcium carbonate & adherence. **DI**: PPI's can ↓ calcium absorption calcium citrate may be better absorbed in this setting. ↓ absorption of: ciprofloxacin, iron, PI HIV, tetracycline, thyroid meds.	Ages 4-8 yrs: 800 mg/d Ages 9-18yrs: 1300 mg/d ♀ > 18 pregnant or lactating: 1000mg/d Pre-menopausal ♀: 1000mg/d Menopausal ♀ & ♂ > 50 yr: **1200mg**/day ♂ 19-50yr: 1000mg/d	~**$50**
	Vit D3 =cholecalciferol, g *X* ▼ 400, 1000, 10,000IU tab; drops; combo with Ca++ Vit D_2=Ergocalciferol **X**; 50,000 cap, liquid. (10,000IU cap; 75,000 cap made from powder) {calcitriol: hypercalcemia risk, ↑cost}	Well tolerated. SE: GI nausea, vomiting, constipation, hypercalcemia. **Vit D3** is preferred over Vit D2 [36] May ↑ muscle strength, ↑ balance & ↓ falls. Risk ↓Vit D: skin dark, sunscreen SPF≥ 8, garment concealing, season, elderly institutionalized, obese, malabsorption, renal or liver dx, non-fish eating, meds anticonvulsants, cholestyramine, HIV, rifampin, steroids, latitude.			Vit D alone/low dose likely does not prevent hip, vertebral, or any new # [37] **Serum** 25-OHD level desired: **>75 nmol/L** 30 ng/mL, ~3months of tx to ↑ level, check level cool season Some recommend **2,000 IU/d** in winter months & 1,000 IU/d in summer. [38] Consider single Vit D loading dose if severely deficient (eg. 75-150,000 IU) Vit D sources: dairy products, salmon, sardines & tuna. Sunscreens ↓↓ Vit D. Sun exposure 5-15min on arm/legs between 10am-3pm 3x/wk often adequate if Caucasian.	Vitamin D3: OP CDN 2010 If < 50 yrs: 400-1000 IU ($10-^{25}$ug)/day If > 50 yrs: **800-2000 IU** ($20-^{50}$ug)/day	~**$30**
HT	**Hormone Therapy** (HT) ♀ -antiresorptive {Males: ♂ with hypogonadism see RxFiles Andropause Testosterone Agents Chart}	**See also RxFiles Postmenopausal Chart page 90** Combo with medroxyprogesterone WHI: ↑CHD/stroke, ↑breast cancer, ↑VTE. [40] Estrogen alone: ↑stroke & DVT (but not CHD or breast cancer).[40] Cognitive impairment & urinary incontinence may worsen.[39] After adjusted analysis hip # data was **not** significant ⇒	NNT = 385 for 5 yrs in ♀ with or without a previous vertebral # [40] WHI	NS compared to placebo arm	HT for symptomatic postmenopausal ♀ as the most effective tx for menopausal Sx relief vasomotor, vaginal atrophy & the prevention of bone loss / #. [2] Consider low conjugated estrogen 0.3mg or micronized estradiol 0.5mg & ultralow ½ of low dose, if both prevent OP & tx menopausal symptoms desired. Inform that it works for OP prevention, but limited data on ↓ of # risk. [2]	CES 0.3mg daily Estrace 0.5mg daily Climara 25ug weekly Estradot 25ug 2x/wk	**84** 96 325 333

New: **Denosumab Prolia** *X* ⊗target RANK ligand inhibits osteoclast, 60mg SC q6month $780 FREEDOM, vertebral # NNT=20, non-vertebral # NNT=67, n=7,868 3yr; HALT; rash, ↓ca^{++}, limb pain, may ↑infection; & ? jaw necrosis & cancer. **Not CDN**: **Strontium** ranelate **Protelos**-2g hs, nausea, diarrhea, seizure, rash DRESS Sx & VTE.
Investigational SERMS: **Bazedoxifene**: 20-40mg/day approved in Europe, SE: ↑vasomotor sx, ↑VTE, leg cramps; **Lasofoxifene**: 0.25-0.5mg PEARL daily SE: ↑VTE but may ↓breast cancer. **Not CDN**: **Ibandronate Boniva** -2.5mg tab daily, 150mg tab po monthly; 3mg IV q3months.

x=non-formulary Sask. ⊗=not on NIHB ☎=EDS-Exception Drug Status Sask 1-800-667-2549 ∅=NIHB prior approval ▼=on NIHB ♀=women ♂=men **#**=fracture **BMD**=bone mineral density **Ca^{2+}**=calcium **CKD**=chronic kidney dx **DVT**=deep vein thrombosis **Dx**=disease **DXA**=dual energy x-ray absorptiometry **FDA**=Food Drug Admin **g**=generic **GIO**=glucocorticoid induced OP **HIV**=Human immunodeficiency virus **Ht**=height ≥2cm/yr loss **Hx**=history **Mg^{2+}**=magnesium **NNT**=number needed to treat **NS**=no significant difference **ONJ**=osteonecrosis jaw **OP**=osteoporosis **OR**=odds ratio **PE**=pulmonary emboli **pl**=placebo **PI**=protease inhibitor **PM**=postmenopausal **PTH**=parathyroid hormone **RR**=relative risk **Scr**=serum creatinine **Sx**=symptom **TSH**=thyroid stimulating hormone **Tx**=treatment **VTE**=venous thromboembolism event **WHO**=World Health Organization **Wt**=weight
Drug Induced OP: ↑ alcohol, antacids aluminum, anticonvulsants carbamazepine, phenobarbital, phenytoin, primidone, aromatase inhibitors anastrozole, letrozole, exemestane, **glucocorticoids** >3 months, drugs causing hypogonadism 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 pioglitazone, rosiglitazone, thyroid hormone excess & Vit A ↑ dose.
Metabolic Non-Osteoporois Bone Diseases: Osteogenesis imperfecta, Osteomalacia, Osteitis fibrosa cystica, **Renal osteodystrophy** check bone specific alkaline phosphatase & PTH; BMD not indicative of dx, ?bone biopsy eg. adynamic bone dx, Osteopetrosis & Paget's dx.

General OP Information: (Screen, BMD, Lab workup…)
Osteoporosis WHO 2002 Defined as T-score ≤ -2.5. Now by # risk.
Prevalence: 2 million OP # in USA in 2005; OP affect 1.4m CDN
Screen: all pts ≥50yr for OP risk factors,
BMD if ♀**≥65yr** ♂≥70yr ACPM'09, or younger PM ♀ or ♂ (50-69yr) if 1major or 2 minor OP risk factor; & BMD (DXA preferred) follow up q2-5yr if moderate risk, or q5-10yr if low risk.
Initial Workup: CBC, alk phos, Scr, Ca, Alb, 25-OH Vit D; elderly (protein electrophoresis if vertebral #, ?myeloma), ♂ testosterone, PTH, xray (thoracic & lumbar), phosphorus, & TSH. Fall hx.
Exam: Hx, X-ray, Ht, Wt, Iliocostal distance, kyphosis; BMD, # 's.
Patient Goal: Tx⇒ stronger bone & ↓ # risk. Prevent fractures!
Education: ↑compliance to meds & bone hygiene treatment.
BMD Tx Follow-up: Do once in 1-3yr after tx started. to catch no responder
If BMD same or ↑, then uncertain when or if repeat BMD.
Use same DXA device if test is repeated.

❷ **Risk Graph according to bone mineral density reporting in Canada CAROC** 2010, 2 (For initial risk assessment)
10-yr risk: **femoral neck** T-score (underestimate risk when lumbar T-score is lower than hip; if spine/hip ≤2.5 at least moderate risk)



Example: Female, age 70, with T-score = -3.5, no hx of fragility fracture, no glucocorticoid use →**HIGH** Risk X marks the spot
Male, age 70, T-score= -3, no hx of fragility # & on **prednisone** 10mg/d >3month → Mod but→**HIGH** Risk b/c of prednisone
Most pts <50yr do **not need** osteoporosis tx unless exceptional circumstance. Both bone quality & density is important.

❸ **FRAX**=fracture risk assessment tool http://www.shef.ac.uk/FRAX/
For untreated pts (white, black, Hispanic & Asian) 40-90yr with osteopenia WHO. BMD is optional for calculating the FRAX risk score.
Canadian & American FRAX dataset is now available.
Input⇒**femoral neck** BMD, age, sex, ht, wt, previous #, if parent hip #, smoker, steroid use, rheumatoid arthritis, 2^0 OP, alcohol ≥3unit/day, ↓BMI
Output⇒Calculates an **ABSOLUTE 10yr hip # & major # probability.**
Consider Treating if: NOT based on BMD or osteopenia only
1) hip or spine **FRACTURE**, or
2) **HIGH RISK** of Fracture: ↓ BMD (♀ PM, ♂ ≥50yr) & ↑ risk
eg. **10yr Risk→hip fracture ≥ 3% or major # ≥ 20% (spine, forearm, shoulder, hip).**

Major Risk Factors: **Age ≥ 65yr**, **Vertebral Compression #**, **Fragility # after age 40yr**, **Family hx** osteoporotic # esp. hip # in mother, Propensity to fall, Osteopenia on radiograph, **Steroid** tx >3months of ≥ prednisone 2.5mg/day, Malabsorption Sx, hyperparathyroidism Primary, Hypogonadism, Early menopause before age 45yr.
Minor Risk Factors: Weight loss of >10% at age 25, weight <60kg, **Smoking** current, Excess alcohol ≥3units/day, Excess caffeine >4cups/day, Low calcium intake, Rheumatoid arthritis, Hyperthyroidism, Anticonvulsant or heparin therapy long term.
Assess Risk: Identify **HIGH risk pts to tx** by ❶ **age, sex, steroid tx, # fragility >40yr & BMD or 10yr Risk** Score like ❷) **Risk Graph** above **or** ❸) **FRAX.** **Low & Moderate Risk** pts usually do **NOT require tx**, except in exceptional circumstances.
10yr ♀ Absolute # Risk: ❶ **HIGH >20%** #→Age T Score=Age 50 T-3.9, Age 55 T-3.4, Age 60 T-3, Age 65 T-2.6, Age 70 T-2.2, Age 75 T-2.1, Age 80 T-2, Age 85 T-2.2. **Low <10%**# or **Moderate 10-20%**# **Risk**: ↑ to **next risk level** if on prednisone ≥2.5mg for >3mon or if fragility # after age 40.
Treat OP with **Calcium & Vit D PLUS First Line Agents**: alendronate, risedronate, zoledronic acid or **Second/Third Line Agents**: raloxifene, calcitonin, etidronate or teriparatide. **Good Bone Care/Hygiene**: Lifestyle (exercise, weight bearing), Vit D, Calcium, & ↓falls / alcohol / smoking.

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Extras

Table: Ten-year absolute fracture risk for women [2] (CAROC basal risk 2010)

Age (years)	Low Risk < 10%	Moderate Risk 10% - 20%	High Risk > 20%
	LOWEST T-SCORE Femoral neck		
50	> - 2.5	- 2.5 to - 3.8	<- 3.8
55	> - 2.5	- 2.5 to – 3.8	< - 3.8
60	> - 2.5	- 2.5 to – 3.8	< - 3.8
65	> - 2.3	- 2.3 to – 3.7	< - 3.7
70	> - 1.9	- 1.9 to – 3.5	< - 3.5
75	> - 1.7	- 1.7 to – 3.2	< - 3.2
80	> - 1.2	- 1.2 to – 2.9	< - 2.9
85	> - 0.5	- 0.5 to – 2.6	< - 2.6
90	> -0.1	- 0.1 to – 2.2	< - 2.2

Table 3: Ten-year absolute fracture risk for men [2] (CAROC basal risk 2010)

Age (years)	Low Risk < 10%	Moderate Risk 10% - 20%	High Risk > 20%
	LOWEST T-SCORE Femoral neck		
50	>-2.5	-2.5 to -3.8	<-3.8
55	>-2.5	-2.5 to -3.9	<-3.9
60	>-2.5	-2.5 to -3.9	<-3.9
65	>-2.5	-2.5 to -3.7	<-3.7
70	>-2.4	-2.4 to -3.7	<-3.7
75	>-2.3	-2.3 to -3.7	<-3.7
80	>-2.3	-2.3 to -3.8	<-3.8
85	>-2.1	-2.1 to -3.8	<-3.8
90	>-2.0	-2.0 to -3.8	<-3.8

There are two risk assessment tools currently available and recommended in the 2010 Canadian OP Guidelines:

1) **CAROC Charts/Graphs**
   (as per tables at left & graphs on previous page)
   ⇨ requires BMD
   http://osteoporosis.bluerush.ca/www/pdf/caroc_oct_2010.pdf

2) **FRAX Canada – Online Calculator**
   ⇨ can be used with OR without a BMD
   http://www.sheffield.ac.uk/FRAX/tool.jsp?country=19

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

References: Osteoporosis Treatment Chart

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Web Links:

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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]