Medications for Osteoporosis:
An Update and Focus on Long Term Care

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Disclosures

- I am an employee of the Fraser Health Authority which receives funding from the British Columbia Ministry of Health's Pharmaceutical, Laboratory and Blood Services Division for the purpose of delivering the BC Provincial Academic Detailing Service
- I have no other conflicts of interest.
- Information provided is a summary of the evidence. The content has been peer-reviewed by clinicians and experts in critical appraisal.

Learning Objectives

- Apply current evidence to guide prescribing and deprescribing decisions for osteoporosis medications with a focus on bisphosphonates and denosumab.
- Consider principal clinical considerations including adverse effects, administration factors and time-to-benefit estimates.
- Review current evidence on vitamin D and calcium supplements pertaining to fracture risk reduction.

Medications for Osteoporosis: An Update

B.C. Provincial Academic Detailing (PAD) Service **August 2024 updated**

Participants will have the opportunity to:

1. Apply current evidence to guide prescribing and deprescribing decisions for bisphosphonates, denosumab, raloxifene, teriparatide and romosozumab.
2. Incorporate fracture risk reduction and time-to-benefit estimates as part of shared-decision making with patients.
3. Compare the principal clinical considerations when choosing between bisphosphonates and denosumab, the most commonly prescribed osteoporosis medications in British Columbia.

Understudied populations in medication clinical trials: Premenopausal females, males, intersex persons, transgender persons, diverse racial or ethnic groups, residents of long term care, multimorbidity and polypharmacy, people taking glucocorticoids, participants defined by FRAX scores.

Brand Name	Generic Name
Fosamax®, Fosavance®	alendronate oral once a day or week
Actonel®, Actonel DR®	risedronate oral once a day or week or month
Aclasta®	zoledronic acid intravenous once a year
Prolia®, Jubbonti®	denosumab subcutaneous every 6 months
Evista®	raloxifene oral once a day
Forteo®, Osnuvo®	teriparatide subcutaneous once a day
Evenity®	romosozumab subcutaneous once a month

BC's Provincial Academic Detailing (PAD) Service is offered free of charge to health care professionals. The service is provided by health authorities and supported by the Ministry of Health. Relevant topics are identified in consultation with various groups. All written materials are externally reviewed by clinicians and experts in critical appraisal.

Osteoporosis medications: indications & basis of approval

Basis of regulatory drug approval for osteoporosis

1. Osteoporosis medications generally enter the market with an indication for use in postmenopausal females based on evidence of a reduction in the risk of radiographic vertebral fractures and, in some cases, clinical (symptomatic) fractures.
2. Subsequent population indications may be added by demonstrating that the medication increases bone mineral density (BMD) – estimates of drug effects (efficacy & safety) for these patient groups are less certain.

Health Canada Indications	Postmenopausal females		Males with osteoporosis	Exposure to medications that increase fracture risk		
	Osteoporosis	Osteopenia		Glucocorticoid females, males	Aromatase Inhibitor non metastatic breast cancer	Androgen Deprivation non metastatic prostate cancer
bisphosphonates	radiographic vertebral & clinical fractures	BMD ⊕	BMD & radiographic vertebral fractures	BMD †		
denosumab ∗	radiographic vertebral & clinical fractures		BMD	BMD ††	BMD ⊕	BMD & radiographic vertebral fractures
raloxifene	radiographic vertebral fractures	BMD				
teriparatide ∗	radiographic vertebral & clinical fractures		BMD	BMD †††		
romosozumab ∗	radiographic vertebral & clinical fractures					

surrogate outcomes: radiographic vertebral factures and bone mineral density, used in osteoporosis medication clinical trials as a substitute for a direct measure of how a patient feels, functions or survives;
radiographic vertebral fractures: detected on scheduled imaging during the clinical trial, may not be symptomatic;
∗ high risk: indicated for those with a history of osteoporotic fracture or multiple risk factors for fracture; ⊕ postmarketing trial(s) demonstrate reduction in clinical fractures; † prednisone ≥ 7.5 mg per day equivalent irrespective of baseline BMD or fracture history; †† prednisone ≥ 7.5 mg per day equivalent plus prior fracture or low BMD; ††† prednisone ≥ 5 mg per day equivalent plus prior fracture or low BMD

Health Canada Drug Product Database; Health Canada Drug Health Product Register; US FDA Approved Drugs; US FDA 2015 public workshop osteoporosis drug development; US FDA table surrogate endpoints drug approval; KEHOE Br J Clin Pharmacol 2019; REID NEJM 2018 osteopenia zoledronic acid; B.C. Ministry of Health 2023 denosumab

B.C. PharmaCare coverage & annual drug cost

Approximate annual drug cost		PharmaCare coverage	Special Authority Criteria
alendronate Fosamax, Fosavance **risedronate** Actonel	$100 ✱	Regular benefit	
zoledronic acid Aclasta	$390 ◆	Limited Coverage	1. osteoporotic fracture *plus* contraindication to oral bisphosphonate – abnormalities of the esophagus such as stricture or achalasia
denosumab Prolia, Jubbonti	$420 biosimilar $950 brand	Limited Coverage biosimilar only	1. osteoporotic fracture *plus* contraindication to oral bisphosphonate – abnormalities of the esophagus such as stricture or achalasia or immune-mediated hypersensitivity reaction 2. aromatase inhibitor for breast cancer (5-year coverage)
raloxifene Evista	$200	Limited Coverage	1. osteoporotic fracture *plus* intolerable adverse effects to oral bisphosphonate *or* unsatisfactory response (postmenopausal females only) – esophageal ulceration, erosion or stricture, lower gastrointestinal symptoms severe enough to cause discontinuation of bisphosphonates after ≥ 1 month trial – new clinically or radiographically documented osteoporotic fracture after 1 year of adherence to alendronate or risedronate
romosozumab Evenity	$8900	Limited Coverage	1. osteoporotic fracture *and* treatment naïve *plus* FRAX score ≥ 20% (postmenopausal females only; 1-year coverage)
teriparatide Forteo, Osnuvo	$8000 biosimilar $8000 brand	Non-benefit	

✱ approximate wholesale cost of weekly generic formulation (alendronate 70 mg, risedronate 35 mg); daily (alendronate 5 & 10 mg, risedronate 5 mg), monthly (risedronate 150 mg), delayed release (risedronate 35 mg DR) formulations are more costly; see **BC PAD Osteoporosis Drug Table** for doses, costs, coverage; ◆ excludes infusion costs and potential missed work hours for working patients

Osteoporosis medications: evidence overview

Postmenopausal females§	Hip fracture	Symptomatic vertebral fracture†	Symptomatic fracture††	Radiographic vertebral fracture†††	Serious adverse events	Withdrawals due to adverse events
bisphosphonate vs **placebo**; 3 – 4 yrs; meta-analysis baseline VF 0% – 100%	**ARR 0.6%** RRR 36%	**ARR 1.8%** RRR 62% ∗	**ARR 2.4%** RRR 21% ∗	**ARR 5.6%** RRR 51% ∗	NSS	NSS
denosumab vs **placebo**; 3 yrs; 1 RCT baseline VF 23%	**ARR 0.5%** RRR 40%	**ARR 1.8%** RRR 69%	**ARR 1.5%** RRR 20%	**ARR 4.9%** RRR 68%	NSS	NSS
raloxifene vs **placebo**; 3 yrs; meta-analysis baseline VF 37% – 56%	NSS	NSS	NSS	**ARR 2.8%** RRR 41%	NSS	**ARI 1.5%**
teriparatide vs **oral bisphosphonate**; 2 yrs; 1 RCT baseline VF 100%	NSS	**ARR 2.8%** RRR 71%	**ARR 4.6%** RRR 52%	**ARR 6.6%** RRR 56%	NSS	NSS
romosozumab vs **oral bisphosphonate**; 2 – 3 yrs; 1 RCT baseline VF or HF 100%	**ARR 1.2%** RRR 38%	**ARR 1.2%** RRR 59%	**ARR 3.3%** RRR 27%	**ARR 3.9%** RRR 50%	NSS	NSS

American College of Physicians 2023 Recommendations for Postmenopausal Females with Osteoporosis: bisphosphonates initial pharmacologic therapy (high certainty); denosumab second line (moderate certainty); romosozumab (moderate certainty) or teriparatide (low certainty) followed by a bisphosphonate in females at very high risk of fracture due to age and fracture history; raloxifene not recommended; **Males with Osteoporosis:** extrapolated from evidence for postmenopausal females: bisphosphonates initial pharmacologic therapy (low certainty); denosumab second line (low certainty)

§ primary osteoporosis: based on BMD or fragility fracture, not secondary to another medical condition or medication; **VF HF** proportion of participants with a vertebral or hip fracture at baseline; **†** clinically recognized, symptomatic; **††** symptomatic nonvertebral ± vertebral fractures excl. fractures not related to osteoporosis; **†††** detected on scheduled imaging, may not be symptomatic, radiographic criteria may vary between trials; **ARR** absolute risk reduction; **ARI** absolute risk increase; **RRR** relative risk reduction; **NSS** not statistically significantly different; **∗ bisphosphonates** heterogeneity in baseline fracture risk across RCTs & variability in estimates of drug effect; **teriparatide** 58% participants previously used a bisphosphonate; **romosozumab** sequential therapy romosozumab for 1 year followed by alendronate for 1 year; 6% participants previously used a bisphosphonate

ACP 2023 osteoporosis guideline & systematic review; FREEDOM NEJM 2009 denosumab; VERO Lancet 2018 & Osteo International 2020 teriparatide vs risedronate; ARCH NEJM 2017 romosozumab vs alendronate; US FDA 2019 romosozumab review; Health Canada 2019 romosozumab review; European Medicines Agency 2020 romosozumab review

Bisphosphonates, denosumab: patient population estimates

Secondary versus Primary Prevention: Alendronate, Denosumab					
Postmenopausal females		**Radiographic vertebral fracture†**			**Participant Demographics**
alendronate	secondary prevention previous vertebral fracture	**ARR ~7%**	3 years	placebo 15.0% → drug 8.0%	▪ ages 55 – 81; ambulatory; self rated health good to excellent ▪ BMD T score –2.0 or lower; mean age 71; 97% White
	primary prevention without previous fracture	**ARR ~2%**	4 years	placebo 3.8% → drug 2.1%	▪ ages 54 – 81; ambulatory; self rated health good to excellent ▪ BMD T score –1.6 or lower; mean age 68; 97% White
denosumab	secondary prevention previous vertebral fracture	**ARR ~9%**	3 years	placebo 13.6% → drug 4.6%	▪ ages 60 – 90; ambulatory; generally in good health ▪ BMD T score –2.5 to –4.0; mean age 72; 93% White ▪ excluding those who had taken a bisphosphonate for > 3 years or within the previous year
	primary prevention without previous fracture	**ARR ~4%**		placebo 5.2% → drug 1.7%	

Patient Populations: Bisphosphonates						
Population	**Radiographic vertebral fracture†**			**Hip fracture**		
postmenopausal females with osteoporosis	**NNT 20 (16 − 27)** baseline risk: ~10%	3 − 4 years	1205 events in 16,902 females	**NNT 143 (105 − 333) ∗** baseline risk: ~2%	3 − 4 years	263 events in 16,634 females
males with osteoporosis	**NNT 33 (26 − 125) ∗** baseline risk: ~5%	2 years	55 events in 1692 males	not estimable		∗ NNT estimate may include sufficient imprecision to impact clinical or patient decisions
people taking glucocorticoids	**NNT 30 (20 − 143) ∗** baseline risk: ~8%	1 − 2 years	77 events in 1343 people	not estimable		

† detected on scheduled imaging, may not be symptomatic; **ARR** absolute risk reduction; **baseline risk + estimates of drug effect** mean difference between drug and placebo for radiographic vertebral fractures varies by baseline risk (e.g., primary vs secondary prevention); this is less apparent for hip fractures where the drug effect varies minimally across trials; **NNT** number of people who need to take a bisphosphonate for one less person to experience a fracture with 95% confidence interval

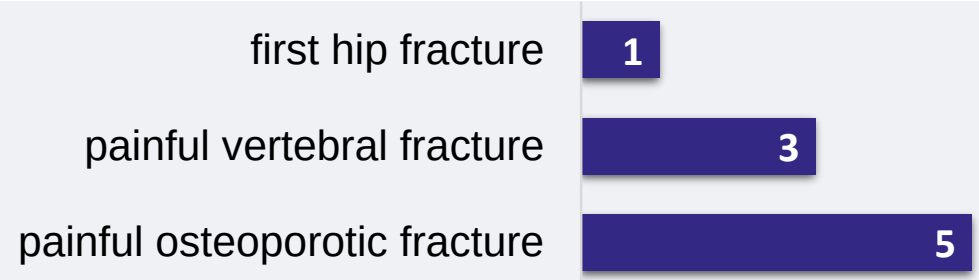
FIT 1 Lancet 1996 alendronate; FIT 2 JAMA 1998 alendronate; FREEDOM NEJM 2009 & J Bone Min Res 2012 denosumab; ACP 2023 osteoporosis guideline & systematic review; COCHRANE 2016 CD001347

Bisphosphonates: shared decision making

Preventing another fracture

You are a postmenopausal female in good health with osteoporosis and you've had a vertebral fracture[1]

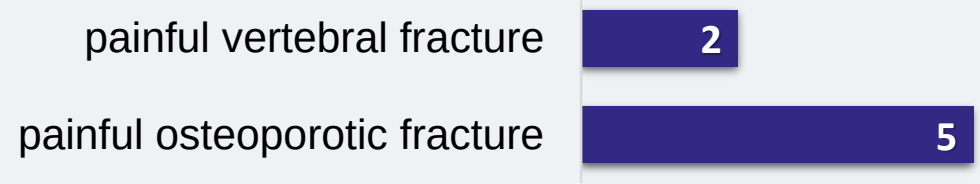
number of people out of **100** estimated to benefit over **3 years**



Preventing another fracture

You are aged 50 or older and you have recently had surgery for an osteoporotic hip fracture[2]

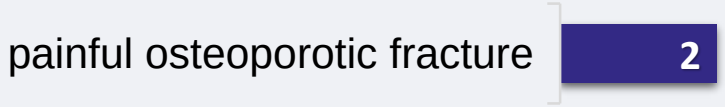
number of people out of **100** estimated to benefit over **2 years**



Preventing a first fracture

You are a postmenopausal female in good health with osteoporosis and you've not had a fracture[3]

number of people out of **100** estimated to benefit over **4 years**



painful osteoporotic fracture: fracture of the vertebrae or another bone considered related to osteoporosis

[1]FIT 1 NEJM 1996 alendronate, CADTH 2021; [2]HORIZON RFT 2007 zoledronic acid; [3]FIT2 JAMA 1998 alendronate, GATES Systematic Rev 2023 alendronate, moderate certainty

Older adults with frailty & multimorbidity

Representation of people with frailty and multimorbidity

- Mean age of participants across trials: 50 – 85 years
- People with multimorbidity, polypharmacy and persons in long term care are underrepresented in osteoporosis trials
- Canadian guideline pharmacotherapy recommendations on the prevention of fractures in long term care are extrapolated from ambulatory, community dwelling females with few or no comorbidities (Osteoporosis Canada 2015)
- A 2023 systematic review of osteoporosis medications did not find evidence for fracture related mortality, functionality or disability

Consider as part of medication decision making

1. **Time-to-benefit:** onset of symptomatic or hip fracture risk reduction and its relevance to people of advanced age or limited life expectancy
   - bisphosphonates: approximately after 12 months of treatment
   - denosumab: approximately after 6 – 12 months of treatment
2. **Administration instructions:** that make it difficult to provide medications safely
3. **Kidney function:** which may preclude medication use or increase the risk of adverse events

Administration		
alendronate	≥ 200 mL plain water	take on empty stomach upon arising for the day; contraindicated = inability to sit or stand upright for at least 30 minutes, abnormalities of the esophagus
risedronate	≥ 120 mL plain water	
zoledronic acid	≥ 500 mL of fluids before & after infusion	infusion not less than 15 minutes; check serum calcium before each dose
denosumab	subcutaneous injection: upper arm, upper thigh, abdomen	check serum calcium before each dose

Kidney	
alendronate	contraindicated: CrCl < 35 mL/min
risedronate	not recommended: CrCl < 30 mL/min
zoledronic acid	contraindicated: CrCl < 35 mL/min (C-G formula using actual body weight)
denosumab	significantly increased risk of hypocalcemia: CrCl < 30 mL/min

HANDEL BMJ 2023; ACP 2023 osteoporosis guideline & systematic review; Osteoporosis Canada 2015 guideline; GATES Systematic Rev 2023; DEARDORFF JAMA Int Med 2022; FIT 1 Lancet 1996 alendronate; HIP NEJM 2001 risedronate; HORIZON PFT & RFT NEJM 2007 zoledronic acid; REID NEJM 2018 zoledronic acid; FREEDOM NEJM 2009 denosumab; Health Canada Drug Product Database

Exit strategies & transitions

Persistence of effect

- Treatment effects of bisphosphonates may persist for years after treatment discontinuation
- Denosumab, teriparatide and romosozumab have a more rapid offset of effect following discontinuation

Bisphosphonates Concern:

longer treatment duration increases the risk of atypical femoral fractures and osteonecrosis of the jaw, although both are rare

- In postmenopausal females, if alendronate is continued for another 5 years after 5 years of initial therapy:
  - symptomatic vertebral factures: ARR 3%
  - atypical femoral fractures: ARI 0.1% – 0.4%
- Osteoporosis Canada 2023 suggests (weak recommendations):
  - initial therapy for 3-6 years (low-certainty evidence)
  - BMD measurement 3 years after initiating pharmacotherapy (very low-certainty evidence)
- Health Canada & US FDA: optimal duration of therapy has not been determined

Denosumab Concern:

discontinuing denosumab is associated with an increased risk of multiple vertebral fractures

- Rate of multiple vertebral fractures (starting 7 months after last dose):
  - placebo: 3.6 per 100 patient years
  - denosumab taken for 1-3 years: 3.0 per 100 patient years
  - denosumab taken for > 3 years: 7.5 per 100 patient years
- Consistency with the every 6 months dosing schedule is important
- Osteoporosis Canada suggests: long-term uninterrupted therapy; if discontinuing after ≤ 4 doses, transition to a bisphosphonate; if discontinuing after ≥ 5 doses, seek advice from a consultant with osteoporosis expertise

Teriparatide Concern:

risk of osteosarcoma in animal studies but postmarketing studies in humans do not find a clinical signal of osteosarcoma

- Transition to a bisphosphonate or denosumab typically considered after 24 months of teriparatide
- US FDA 2020 review: evidence no longer supports a warning for osteosarcoma
- Health Canada & US FDA: continue beyond 24 months of lifetime exposure only if high risk for fracture

Romosozumab Concern:

effects on bone mineral density and bone formation markers wane after 12 months of treatment

- Transition to a bisphosphonate or denosumab typically considered after 12 months Health Canada & US FDA: limit treatment duration to 12 months

Health Canada Drug Product Database; US FDA Approved Drugs; AHRQ 2019 osteoporosis long term drug therapy; FLEX extension trial JAMA 2006 alendronate; BLACK NEJM 2020; HORIZON PFT extension trial J Bone Min Res 2012 zoledronic acid; Osteoporosis Canada 2023 guideline; COSMAN J Bone Miner Res 2022 denosumab extension; US FDA 2020 teriparatide review; US FDA 2019 romosozumab review; REID Lancet 2022

Bisphosphonates: clinical considerations

Contraindications
oral: abnormalities of esophagus, inability to sit or stand upright for at least 30 minutes, inability to swallow ≥ 120 – 200 mL of water
zoledronic acid: inability to appropriately hydrate pre and post infusion
hypocalcemia
CrCl < 35 mL/min: alendronate
CrCl < 30 mL/min: risedronate
CrCl < 35 mL/min: zoledronic acid

Calcium & Vitamin D
zoledronic acid: check serum calcium before each dose – replete calcium and vitamin D if necessary
hypocalcemia symptoms: muscle cramps or twitching, numbness or tingling mouth, fingers or toes

Acute kidney injury
zoledronic acid: ensure adequate hydration (eat & drink normally including at least 500 mL of fluids) prior to and after administration – particularly in older adults, those receiving diuretics or nephrotoxic medications
monitoring CrCl post dose: recommended in patients at risk
infusion time: minimum 15 minutes

Infusion reaction
zoledronic acid: ~25% of patients within 3 days of first infusion, less frequent on subsequent infusions
symptoms: fever, chills, fatigue; musculoskeletal pain; pain & redness at infusion site
acetaminophen or ibuprofen to prevent or manage symptoms

Gastrointestinal
oral: may cause or worsen esophagitis, esophageal ulcers, esophageal erosions, stricture or perforation

Musculoskeletal
bone, joint, muscle pain: possibly severe; also common infusion reaction symptoms

Ophthalmologic
conjunctivitis, uveitis, episcleritis, scleritis: incidence ≤ 1%

Atypical femoral fractures
subtrochanteric or proximal femoral shaft: 1/3 bilateral; may occur in absence of apparent trauma
prodrome: patients should be counselled to report new or unusual thigh, hip, groin pain
incidence: < 0.1% (0 – 5 years)
additive risk factors: duration of therapy > 3 – 5 years, Asian descent, > 1 year of glucocorticoid use

Osteonecrosis of the jaw
associated with invasive dental procedures such as tooth extraction: consider preventive dentistry/regular dental monitoring
incidence: 0.02 – 0.15%
additive risk factors: higher dose oncology regimens, duration of therapy > 2 – 3 years

See reference list

Denosumab: clinical considerations

Contraindications
hypocalcemia

Calcium & Vitamin D
hypocalcemia: rare if normal kidney function and adequate calcium and vitamin D intake
check serum calcium: before each dose (replete calcium and vitamin D if necessary), and within 2 weeks post dose in patients at risk for hypocalcemia
risk factors for hypocalcemia: hypoparathyroidism, thyroid or parathyroid surgery, excision of small intestine, malabsorption syndromes, CrCl < 30 mL/min or dialysis, previous hypocalcemia
hypocalcemia symptoms: muscle cramps or twitching, numbness or tingling mouth, fingers or toes

Chronic kidney disease
no dose adjustment required
insufficient evidence to evaluate fracture efficacy in patients with eGFR < 30 mL/min
risk of hypocalcemia increases as eGFR declines: 30 – 60 mL/min: < 1% 15 – 30 mL/min: 4% < 15 mL/min, dialysis: 24 – 42%

Infection
increase in serious infections leading to hospitalization: ENT, GI, cellulitis; absolute risk increase 0.6% over 1-3 years
caution: patients on glucocorticoids with active infection or history of recurrent or chronic infection

Dermatologic
rashes, dermatitis, eczema: uncommon; discontinue if severe

Multiple vertebral fractures
discontinuing denosumab: associated with an increased risk of multiple vertebral fractures
Osteoporosis Canada suggests long-term uninterrupted therapy or an exit strategy that is dependent on duration of therapy

Musculoskeletal
bone, joint, muscle pain: reported by ~35% in both drug and placebo groups; case reports of severe pain

Biosimilar
approval based on: comparative pharmacology, efficacy, safety
efficacy endpoint in confirmatory clinical study: BMD at 1 year in postmenopausal females
approval was extended to all denosumab indications

Atypical femoral fractures
subtrochanteric or proximal femoral shaft: 1/3 bilateral; may occur in absence of apparent trauma
prodrome: patients should be counselled to report new or unusual thigh, hip, groin pain
incidence: less well documented for denosumab compared to bisphosphonates

Osteonecrosis of the jaw
associated with invasive dental procedures such as tooth extraction: consider preventive dentistry/regular dental monitoring
incidence: 0.05 – 0.7% over 7 –10 years
additive risk factors: higher dose oncology regimens, longer duration of therapy

See reference list

September 2024

Refills

Your dose of drug information in between sessions

Which factors should be considered when prescribing a bisphosphonate for frail or older adults living in long-term care?

Conclusion: Older adults living in long-term care and people with frailty are underrepresented in bisphosphonate clinical trials. In the long-term care setting, consideration should be given to their complex administration instructions, contraindications, and the delayed time-to-benefit.

The BC Provincial Academic Detailing (PAD) service's topic Medications for osteoporosis: an update looks at the evidence for bisphosphonates, denosumab, raloxifene, teriparatide and romosozumab.[1] Click to book a session with an academic detailing pharmacist in your area. We received this question during PAD sessions: **How does the evidence apply to frail or older adults living in long-term care?**

a) **Clinical trial evidence:**[1,2] People with multimorbidity, polypharmacy and persons living in long-term care have been underrepresented in bisphosphonate clinical trials. Recently, the first bisphosphonate fracture trial in ambulatory females living in long-term care was completed (ZEST II). After 3 years, the rate of fractures was similar in the zoledronic acid and placebo groups (1.06 and 1.01 fractures per person-year, respectively).

b) **Time-to-benefit:**[1,3] In clinical trials of healthy, postmenopausal females the onset of symptomatic or hip fracture risk reduction appears approximately 12 months after initiating bisphosphonate treatment. In addition to the results of the ZEST II trial, this might have relevance when prioritizing essential medications for people with limited life-expectancy.

c) **Administration:**[1] Determine if a person with frailty and/or the long-term care facility has the capacity to follow the administration instructions of oral bisphosphonates intended to reduce the risk of esophagitis, esophageal ulcers, erosions, stricture, and perforation. Refer to Table 1.

d) **Renal function:**[1,4] Declining renal function may preclude oral and intravenous bisphosphonate use. Further, the risk of acute kidney injury with zoledronic acid requires adequate hydration, pre and post infusion. Refer to Table 1.

Table 1. Bisphosphonate contraindications & administration instructions[1]

alendronate (Fosamax®, Fosavance®) **risedronate** (Actonel®, Actonel DR®)	**contraindications**	▪ abnormalities of the esophagus ▪ inability to sit or stand upright for at least 30 minutes following administration ▪ inability to swallow ≥ 120 – 200 mL of plain water ▪ hypocalcemia ▪ CrCl < 30-35 mL/min
	administration	▪ take on empty stomach upon arising for the day ▪ avoid taking any other medications (including vitamins and antacids) for at least 30 minutes
zoledronic acid (Aclasta®)	**contraindications**	▪ inability to appropriately hydrate pre and post infusion ▪ hypocalcemia ▪ CrCl < 35 mL/min (C-G formula using actual body weight)
	administration	▪ ≥ 500 mL of fluids before and after infusion ▪ infusion time: minimum 15 minutes

[1]BC PAD Service Medications for Osteoporosis: An Update (December 2023 updated); [2]Zoledronic Acid for Osteoporotic Fracture Prevention (ZEST II) ClinicalTrials.gov NCT02589600; [3]DEARDORFF JAMA Int Med 2022;182:33-41 (PMID:34807231); [4]Health Canada Drug Product Database Aclasta

BC PAD Refills

Vitamin D & calcium supplementation: falls, fractures, severe deficiency

To reduce the risk of fractures or falls – supplements not recommended

- Vitamin D and calcium supplements are not recommended for community dwelling adults who are well nourished and have a low burden of chronic disease

Vitamin D ± calcium supplementation meta analysis (81 RCTs; 53,537 people)		
Majority of trials: community dwelling participants, aged ≥ 65		
Total fracture	**Hip fracture**	**Falls**
RR 1.00 (95%CI 0.93, 1.07)	RR 1.11 (95%CI 0.97, 1.26)	RR 0.97 (95%CI 0.93, 1.02)

Health Canada Dietary Reference Intakes: Adults Aged > 50

Age	Vitamin D		Calcium	
	RDA	UL	RDA	UL
51 – 70 males	600 IU	4000 IU	1000 mg	2000 mg
51 – 70 females	600 IU		1200 mg	
> 70	800 IU		1200 mg	

RDA recommended dietary allowance; meets or exceeds the requirement of 97.5% of the population; 97.5% of the population requires less than the RDA; **UL** upper limit above which risk of adverse events increases; not intended as a target intake; **Vitamin D** RDA estimated under conditions of minimal to no sun exposure; corresponds to 25-OH-D levels 50 nmol/L; **National Academies** "it is impossible to know a given patient's actual requirement and the RDA will nearly always meet the needs of generally healthy people"

To reduce the risk of severe deficiency in people at risk

- 25-OH-D levels < 30 nmol/L are associated with an increased risk of deficiency and its complications (rickets in children, osteomalacia in adults)
- Vitamin D supplementation at doses 400 – 1000 IU per day can be advised for those with risk factors for deficiency
  - Examples: people living in institutions or who are housebound with limited sun exposure, poor nutrition, conditions or medications that affect vitamin D metabolism
- Higher doses that aim to raise 25-OH-D levels > 75 nmol/L do not reduce disease burden and in some trials have increased the risk of fractures, falls, hospitalization, hypercalcemia, hypercalciuria and bone mineral density losses

To reduce the risk of hypocalcemia

- Vitamin D and calcium supplements are often included in the clinical trials of osteoporosis medications but are unlikely to provide additive fracture risk reduction RECORD Trial 2005
- Bisphosphonates and denosumab are contraindicated in people with hypocalcemia
- Check serum calcium before each dose of zoledronic acid and denosumab – replete calcium and vitamin D if necessary

USPSTF 2018 vitamin d calcium supplementation; USPSTF 2018 falls prevention; USPSTF 2021 vitamin d screening; BOLLAND Lancet Diabetes Endocrinol 2018 meta analysis; National Academies 2011 dietary reference intakes vitamin D, calcium; ROSS J Clin Endocrinol Metab 2011; MANSON NEJM 2016; BOLLAND BMJ 2016; REID Nutrients 2020; CUMMINGS NEJM 2022; REID Lancet 2022; GALLAGHER Lancet Diabetes Endocrinol 2023; Health Canada Drug Product Database; RECORD Lancet 2005

v. June 15, 2023



KEY MESSAGES:

1. Identified 1 overview of systematic reviews and 2 systematic reviews.

2. There is a suggestion that for seniors living in long term care, compared to control, Vitamin D supplementation, with or without calcium, may reduce the rate of falls and fractures, but the reductions were not always statistically significant.

3. There were no statistically significant differences in the number of seniors who fell with Vitamin D supplementation with or without calcium, compared with control.

4. Findings need to be interpreted with caution considering the limitations of of the quality of RCTs (very low to moderate).

Vit D doses ranged 100-2200 IU/day/ calcium 300-2000mg/day



TOOLS FOR PRACTICE

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

Vitamin D and Fracture Prevention: Not what it's cracked up to be?

CLINICAL QUESTION

Does vitamin D prevent fragility fractures?

8 systematic reviews (RCTs); 34,000-76,000 mostly community-dwelling women: some with previous fracture, established osteoporosis or metabolic bone disease, followed 9-84 months

BOTTOM LINE

Vitamin D alone does not prevent fractures regardless of dose, vitamin D status or previous fracture. The combination of calcium and vitamin D might reduce the risk of total fractures from 11.5% to 10.9% and hip fractures from 1.8% to 1.5% over 9-84 months, but this benefit may be limited to women in long-term care. Adding calcium increases risk of renal calculi (2.1% to 2.5%).