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Alberta College of Pharmacists

DUE Quarterly

DRUG USE IN THE ELDERLY

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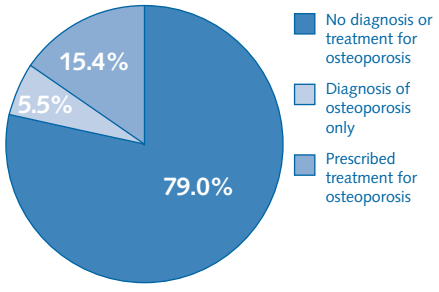
PROMOTING MORE EFFECTIVE MEDICATION USE BY SENIORS

Management of Osteoporosis: An Integrated Approach

In 2010, Osteoporosis Canada published revised clinical practice guidelines for the diagnosis and management of osteoporosis. These guidelines focus on identifying high-risk fragility fracture patients and an integrated management approach. A key shift is in identifying a person's 10-year absolute fracture risk using two closely related assessment tools available in Canada: the Canadian Association of Radiologists and Osteoporosis Canada tool (CAROC) and the Fracture Risk Assessment Tool of the World Health Organization (FRAX). Although low bone-mineral density (BMD) is a risk factor for fragility fractures, it is now recognized that BMD testing alone is insufficient in identifying this high-risk population. Most fragility fractures occur in patients whose BMD is not in the osteoporotic range (i.e., T-score ≤-2.5).

Figure 1. Undertreatment of Osteoporosis Post Fracture in Women



This care gap is even wider in men and those who reside in long-term care.[2,3]

A fracture is to osteoporosis what a heart attack is to cardiovascular disease BUT the treatment gap is far wider post fracture than post MI.[1,4]

1. Bessette L, et al. *Osteoporosis Int* 2008; 19:79-86.
2. Papaioannou A, et al. *Osteoporosis Int* 2008; 19(4):581-587.
3. Giangregorio L, *Osteoporosis Int* 2009; 20(9):1471-8.
4. Austin PC, et al. *CMAJ* 2008; 179(9): 901-908.

In Canada, there is a high prevalence of fragility fractures, which carry a significant burden of mortality and morbidity. Fragility fractures occur more commonly in Canadian women than heart attack, stroke and breast cancer combined.

> A fracture is to osteoporosis what a heart attack is to cardiovascular disease, BUT the treatment gap is far wider post-fracture than post-MI.

Osteoporotic fractures consume more hospital bed days than stroke, diabetes or heart attack. These fractures negatively impact quality of life as they affect self-care, mobility and chronic pain. Less than 40% of those who experience a hip fracture return to their prior walking abilities. Only 44% of people hospitalized with hip fractures are discharged home, while 10% are transferred to another hospital, 27% to rehabilitation centers and 17% to long-term care facilities. In addition, 28% of women and 37% of men who suffer a hip fracture will die within the following year.

Assessment for osteoporosis and fracture risk

To determine appropriate prevention or treatment strategies, patients must first be screened and fracture risk assessed. Risk factors for osteoporosis and fracture in those 65 years+ should be identified (Table 1). A person's 10-year absolute fracture risk can be determined using CAROC and/or FRAX. CAROC requires a BMD T-Score while FRAX does not.

Table 1. Recommended Elements of Clinical Assessment

HISTORY	**Identify risk factors for low bone-mineral density (BMD), future fractures and falls** • Prior fragility fractures • Parental hip fracture • Glucocorticoid use • Current smoking • High alcohol intake (≥ 3 units per day) • Rheumatoid arthritis • Inquire about falls in the previous 12 months • Inquire about gait and balance

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NEXT ISSUE

- Osteoarthritis

DUE Quarterly offers expert opinions — not ACP-AMA guidelines or evaluations of drug use.

Remember these tools are for treatment-naïve patients and those at least 50 years old. A CAROC mobile app is available to download from www.osteoporosis.ca and an online FRAX tool can be found at http://www.sheffield.ac.uk/FRAX/tool.jsp?country=19.

A 10-year absolute fracture risk can be categorized as **low** (<10%), **moderate** (10-20%) or **high** (>20%) using CAROC or FRAX. The greatest benefit for fracture risk reduction with pharmacotherapy has been demonstrated in the **high-risk** population. **Low-risk** patients are unlikely to benefit from pharmacotherapy; however, risk should be reassessed every five years if they remain at low risk. The osteoporotic fractures incidence is high in the **moderate-risk** category; therefore, consider risk factors and patient preference when determining pharmacotherapy.

Table 2. Recommended Biochemical Tests for Patients Being Assessed for Osteoporosis

- Calcium, corrected for albumin
- Complete blood count
- Creatinine
- Alkaline phosphatase
- Thyroid-stimulating hormone
- Serum protein electrophoresis (for patients with vertebral fractures)
- 25-Hydroxyvitamin D*

**Should be measured after three to four months of adequate supplementation and should not be repeated if an optimal level (at least 75 nmol/L) is achieved.*

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Recommended biochemical tests for osteoporosis assessment can be found in Table 2. Consider additional biochemical testing to rule out secondary causes of osteoporosis in patients based on clinical assessment and those with continued bone loss despite treatment. A lateral spine X-ray is recommended for patients with significant height loss (i.e., historical >6 cm or prospective >2 cm over one to three years) and dorsal kyphosis to rule out vertebral compression fractures.

Fall risk

In the elderly, falling is an independent risk factor for fracture. Fall history should be assessed and if previous falls are present, a multifactorial risk assessment is useful. Risks can be categorized as biological (e.g., medical/mobility issues and age-related changes), medication related (e.g., type and quantity), environmental (e.g., hazards in the home), social/economic (e.g., living alone) and behavioral (e.g., alcohol intake). Reducing medication number and/or dosage, and prioritization of psychotropic medications and discontinuation/reduction is important in the elderly.

Treatment

Lifestyle: Lifestyle modifications are recommended for all at-risk or osteoporosis patients. Weight-bearing exercise and resistance training can improve quality of life, muscle strength and balance. Core stability exercises are recommended for those with vertebral fractures. Fall prevention programs should be considered for those at increased risk.

Calcium (see Table 3)*:* The current recommendation for seniors is 1,200 mg of elemental calcium from both dietary sources and supplements. For optimal absorption, calcium supplements should be given in divided doses and calcium carbonate, in particular, requires administration with meals. Calcium citrate can be with or without meals and is preferred in patients with achlorhydra and/or use of a proton-pump inhibitor (PPI). Supplements should be considered only when dietary intake is below the recommended level.

Table 3. Vitamin D

- Adequate vitamin D status, in addition to calcium from diet and supplements (total 1,200 mg daily), is essential for the prevention and treatment of osteoporosis.
- In healthy adults under 50 years old, routine vitamin D supplementation (D3) 400-1,000 IU (10-25 mcg) per day is recommended. Serum 25-OH-D should not be measured.
- Adults over 50 years old are at moderate risk for vitamin D deficiency. Supplementation with at least 800-1,000 IU (20-25 mcg) of vitamin D daily is recommended. To achieve optimal vitamin D status, supplementation greater than 1,000 IU (25 mcg) per day may be required. Daily doses up to 2,000 IU (50 mcg) are safe and do not require monitoring.
- In individuals receiving pharmacologic therapy for osteoporosis, measurement of serum 25-OH-D should follow three to four months of an adequate vitamin D supplementation dose and should not be repeated if an optimal level (25-OH-D ≥ 75 nmol/L) is achieved.

Calcium supplementation has been associated with an increased risk of cardiovascular events in older women. A 31% risk increase was found in a meta analysis that included trials in which patients were taking supplements of at least 500 mg calcium carbonate daily, but not necessarily taking vitamin D. These trials were not designed specifically to evaluate cardiovascular outcomes and baseline dietary intake of calcium ranged from 750 mg to 1,240 mg daily. The mechanism for this potential risk remains unclear.

Vitamin D: See Table 3.

Calcium and vitamin D should not be used as the sole osteoporosis treatment in high-risk individuals as dietary changes alone may not be enough to prevent bone loss.

Pharmacotherapy: Medications currently approved in Canada include anti-resorptive agents and one anabolic agent. In addition to oral bisphosphonates, hormone therapy and teriparatide, there are newer agents available such as the RANK ligand inhibitor (denosumab) and the IV bisphosphonate (zoledronic acid). All these agents have proven benefits in fracture prevention. First-line agents are those shown to reduce hip and vertebral fractures. Access to some of these agents in Alberta may be restricted or require special authorization (SA) through Alberta Blue Cross (ABC).

Monitoring therapy: Repeat BMD no sooner than two years after therapy initiation, then every two to five years while on pharmacotherapy. If etidronate is being used, repeat BMD measurement after one year as per ABC SA criteria.

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Practically speaking . . .

Integrated Management Model

Encourage **basic bone health** for all individuals including: regular active weight bearing exercise, calcium (diet and supplements) 1200 mg daily, vitamin D: 800 - 2000 IU daily after age 50 (400 - 1000 for those <age 50 at low risk), and fall prevention strategies.

Age <50

- Fragility fractures
- High-risk medication use
- Hypogonadism
- Malabsorption syndromes
- Chronic inflammatory conditions
- Primary hyperparathyroidism
- Other disorders strongly associated with rapid bone loss and/or fractures

Age 50 - 64

- Fragility fracture after age 40
- Prolonged glucocorticoid or other high-risk medication use
- Parental hip fracture
- Vertebral fracture or osteopenia identified on X-ray
- High alcohol intake or current smoking
- Low body weight (< 60 kg) or major weight loss (>10% of weight at age 25)
- Other disorders strongly associated with osteoporosis

Age ≥65

- All men and women

Initial BMD Testing

Fracture Risk Assessment

Low Risk	Moderate Risk	High Risk
10-year fracture risk <10%	10-year fracture risk 10 - 20%	10-year fracture risk > 20% or Prior fragility fracture of hip or spine or More than one fragility fracture
Unlikely to benefit from pharmacotherapy *Reassess risk in 5 years*	*Lateral thoracolumbar x-ray (T4-L4) or vertebral fracture analysis (VFA) may aid in decision-making by identifying vertebral fractures*	

Factors that Warrant Consideration for Pharmacological Therapy:

- Additional vertebral fracture(s) identified on VFA or lateral spine X-ray
- Previous wrist fracture in individuals older than age 65 or those with T-score ≤ -2.5
- Lumbar spine T-score much lower than femoral neck T-score
- Rapid bone loss
- Men receiving androgen-deprivation therapy for prostate cancer
- Women receiving aromatase-inhibitor therapy for breast cancer
- Long-term or repeated systemic glucocorticoid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic glucocorticoid use
- Recurrent falls defined as falling 2 or more times in the past 12 months
- Other disorders strongly associated with osteoporosis, rapid bone loss or fractures

Repeat BMD in 1-3 years and reassess risk

Always consider patient preference

Good evidence of benefit from pharmacotherapy

Adapted from Papaioannou A et al. Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ* 2010 http://www.cmaj.ca/cgi/doi/10.1503/cmaj.100771.

First Line Therapies with Evidence for Fracture Prevention in Postmenopausal Women*

Type of Fracture	Antiresorptive Therapy						Bone Formation Therapy
	BISPHOSPHONATES			DENOSUMAB	RALOXIFENE	ESTROGEN** (HORMONE THERAPY)	TERIPARATIDE
	Alendronate	Risedronate	Zoledronic Acid				
Vertebral	✓	✓	✓	✓	✓	✓	✓
Hip	✓	✓	✓	✓	-	✓	-
Non-vertebral†	✓	✓	✓	✓	-	✓	✓

† In Clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.
* For postmenopausal women, ✓ indicates first line therapies and Grade A recommendation. For men requiring treatment, alendronate, risedronate, and zoledronic acid can be used as first-line therapies for prevention of fractures (Grade D).
** Hormone therapy (estrogen) can be used as first-line therapy in women with menopausal symptoms.

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	Antiresorptive Therapy				Bone Formation Therapy
	Bisphosphonates Alendronate (A) Risedronate (R) Zoledronic Acid (ZA)	Denosumab RANK ligand inhibitor	Raloxifene Selective estrogen receptor modulator	Estrogen/HRT	Teriparatide Recombinant PTH
Mechanism of Action	• Analogue of pyrophosphate, binds to hydroxyapatite in bone • Inhibits osteoclast-mediated bone resorption	• Inhibitor of RANK ligand • Prevents osteoclast formation and decreases bone resorption	• Estrogen agonist in bone and lipids • Estrogen antagonist in breast and uterus	• Affects bone resorption by reducing osteoclast number and activity	• Anabolic effect • Stimulates osteoblast function • Affect on calcium homeostasis
Specific Therapeutic Uses	• Glucocorticoid induced osteoporosis: fracture prevention in men and women • Maintain BMD with aromatase inhibitors and androgen deprivation therapy	• Maintain BMD with aromatase inhibitors and androgen deprivation therapy	• Effective for post-menopausal osteoporosis • May reduce risk of breast cancer	• Reduction of menopausal symptoms in addition to fracture prevention	• Glucocorticoid induced osteoporosis in men and women • Patients who fail or are intolerant to previous osteoporosis therapy • Severe osteoporosis
Adverse Effects/ Cautions	• GI irritation with oral formulations • Bone/muscle/joint pain • Hypocalcemia • Osteonecrosis of the jaw (ONJ) • Atypical or subtrochanteric fracture • Renal impairment (avoid with creatinine clearance <35 ml/min)	• Dermatological (cellulitis/eczema) • Hypocalcemia • ONJ • Dose adjustment is not required with reduced renal function	• May increase risk of VTE • Exacerbates hot flashes • Leg cramps	• Increased risk of stroke, VTE and breast cancer • Increase CHD in combination with progesterone therapy • Endometrial hyperplasia with unopposed estrogen therapy	• Dizziness (rare risk of orthostatic hypotension) • Contraindicated: hypercalcemia, metabolic bone disease other than primary osteoporosis, severe renal impairment
Dose	A: 10mg/d; 70 mg/wk R: 5 mg/d; 35 mg/wk; 150mg/mo Z: 5 mg IV q year	• 60 mg SC every 6 months • Drug holiday not recommended due to loss of antiresorptive effect.	60 mg once daily	Standard dose: conjugated estrogen 0.625 mg or equivalent +/- progestin (e.g., MPA)	20 ug SC daily for a maximum of 24 months
Comments	A/R: SA for ABC Z: SA; ABC coverage for Paget's disease only Z: Ensure hydration before and after infusion	SA required for ABC	• Data for vertebral compression fracture only • Avoid in women with CVD and dyslipidemia	• Risk may outweigh benefit • Effective for vasomotor symptoms in menopausal women	Not covered by ABC

Specific issues

- **Medication induced osteoporosis:** Bone loss from glucocorticoid treatment can occur within three to six months with fracture risk increasing with doses of prednisone as low as 2.5-7.5 mg per day. Alendronate, risedronate and teriparatide have been shown to reduce vertebral fractures and increase BMD for patients taking glucocorticoids. Treatment is recommended in those taking ≥ 7.5 mg prednisone per day for at least three months. Bisphosphonates and denosumab maintain BMD in those taking aromatase inhibitors for breast cancer and androgen deprivation therapy for prostate cancer. In these patients, fracture risk should be assessed and pharmacotherapy considered.
- **Osteonecrosis of the jaw:** ONJ is an area of exposed bone in the mandible or maxilla. It is extremely rare (i.e., 1 per 10,000 patients). Rates are higher in malignancy, those undergoing chemotherapy or radiation treatment, high-dose bisphosphonates, diabetes, poor dental hygiene and invasive dental procedures (e.g., tooth extraction or implants). Connection with antiresorptive therapy (bisphosphonates and denosumab) is controversial. Good dental hygiene is recommended for all patients.
- **Atypical (subtrochanteric) fracture:** Though extremely rare, they may be more common in patients taking long-term bisphosphonate therapy, though a definitive link has not been established. These appear as 'chalk-like' breaks and patients may present with prodromal thigh or groin pain, which should trigger radiography and/or bone scanning in those on long-term bisphosphonates. Atypical fractures do occur in patients not exposed to bisphosphonates. It is important to remember that a patient with a high osteoporosis risk has a much greater chance of developing a typical hip fracture than an atypical one. Less than 1% of femoral fractures are atypical.
- **Esophageal cancer:** Risk does not appear to increase in patients taking bisphosphonates compared to those who do not.
- **Osteogenic sarcoma:** This concern was raised due to an elevated incidence seen in rats treated with high doses of teriparatide. Worldwide there have been close to one million patients who have taken or are on teriparatide with only three reported cases of osteosarcoma, a rate that is similar to that of the general population.
- **Drug holidays:** There is no agreement on optimal bisphosphonate duration in osteoporosis. An FDA panel agreed that there wasn't enough evidence to warrant recommending a drug holiday as a treatment plan. Reduced vertebral fracture risk is seen in those who maintain bisphosphonate therapy after five years, compared to those who do not. For high-risk fracture patients it is recommended to continue therapy without a drug holiday.
- **Adherence:** A 50% adherence to bisphosphonate therapy results in BMD that is similar to no treatment at all. Oral bisphosphonates bioavailability is low, therefore correct administration is essential.
- **Bisphosphonates:** Bisphosphonates need to be separated by medications and food to avoid binding in the GI tract and poor absorption. This may be a concern in long-term care facilities, home care and other places where pills are blister-packed and may not be separated from each other or from meals. A new 'delayed release' risedronate formulation delivers medication to sites beyond the stomach where absorption interference is likely lower. A 35 mg weekly does should be taken after meals and may be a suitable alternative.
- **Formulation:** Oral bisphosphonates may cause esophageal irritation or ulceration and should not be used in patients with difficulty swallowing, GERD or esophageal stricture. Injectable formulations may be considered in these situations.
- **Risk versus benefit:** For patients with high 10-year fracture risk, the pharmacotherapy benefits far outweigh potential risks of medication side effects.
- **Compassionate programs:** Many medications approved in Alberta are not covered by ABC. There are programs available from manufacturers that may facilitate access to medication and administration.

References available online.

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