Pharmacologic management of osteoporosis

BONE UNDERGOES A CONSTANT PROCESS OF REMODELING BY OSTEOCLAST cells that break down (or resorb) old bone and osteoblast cells that synthesize new bone. Osteoporosis and most other adult skeletal diseases are due to excessive osteoclast activity that leads to an imbalance in this process and a net bone loss.[1] Pharmacologic therapies for osteoporosis (Table 1) act on bone remodeling either by reducing bone resorption or stimulating bone formation.

Recent advances in the knowledge of bone biology at the molecular and cellular levels have led to greater understanding of bone pathophysiology and the development of new treatment agents.[2]

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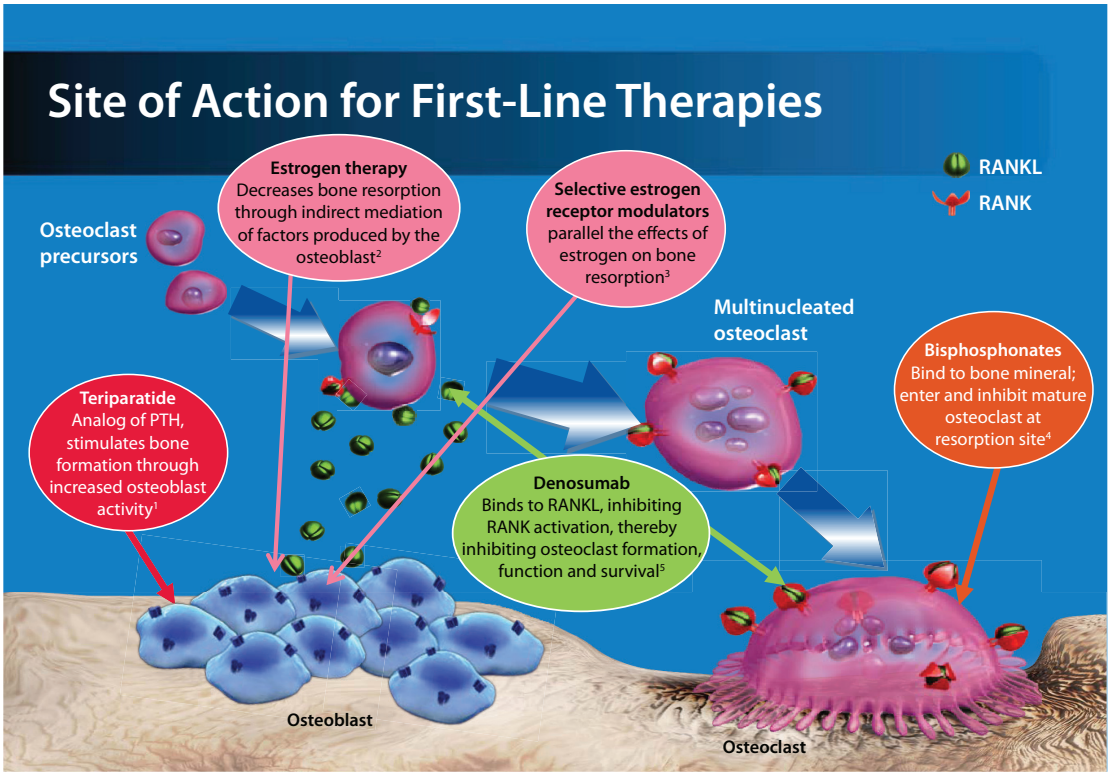

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TABLE 1 Pharmacologic management of osteoporosis[1]

Adapted with permission from: Hanley DA. Osteoporosis. Available: www.e-therapeutics.ca.

Drug	Dose	Adverse effects	Comments
Nutritional supplements			
calcium Caltrate 600, Os-Cal, Tums, generics	Men <50 y, and premenopausal, pregnant or lactating women: 1000 mg/day. Men >50 y and postmenopausal women: 1200 mg/day	Constipation and nausea are the most common side effects. Other possible side effects include hypercalcemia, hypercalciuria, renal calcification, renal stones and ↑ risk of myocardial infarction.	Doses represent the *total intake from diet and supplements.* Calcium carbonate is most often recommended as it is inexpensive and is available in many dosage forms. Both natural (e.g., from oyster shells) and synthetically produced are equally effective. The carbonate salt requires an acidic environment for proper absorption and should be taken with meals. Individuals who may have decreased acid secretion, such as those taking H_2-receptor antagonists (e.g., ranitidine) or proton pump inhibitors (e.g., pantoprazole), should consider using calcium citrate, as its absorption is not affected by these agents.[2]
vitamin D	For D_3: 800–2000 IU daily for those at high risk and adults >50 y; 400–1000 IU for those at low risk and adults <50 y[3]	Possible side effects are hypercalcemia, hypercalciuria, renal calcification and renal stones (usually at very high doses).	Doses represent the *total intake from diet and supplements* in patients with OP. Increases calcium absorption. Many multivitamin supplements contain 400 IU vitamin D and are a commonly used preparation. Vitamin D_3 (cholecalciferol) is preferred over vitamin D_2 (ergocalciferol).
Oral bisphosphonates			
etidronate Generics	Prevention & treatment of OP in postmenopausal women, prevention & treatment of corticosteroid-induced OP in women & men and treatment (to ↑ BMD) of primary OP in men: 400 mg/day × 14 days. Calcium alone days 15-90. Repeat	Side effects are usually minimal: GI symptoms, altered taste, nighttime leg cramps. Very rarely reported: acute-phase reactions involving fever and lymphopenia, joint or muscle pain, skin reactions, ocular effects. Safety in impaired renal function (ClCr <35 mL/min) is unknown.	Etidronate should be taken on an empty stomach with a full glass of water. To aid adherence, it is recommended that patients take the therapy at bedtime, at least 2 h before or after eating. Calcium supplements should be separated by at least 2 h before or after.
alendronate Fosamax, generics	Treatment in postmenopausal women & men: 10 mg/day or 70 mg once weekly Treatment and prevention of glucocorticoid-induced OP in men & women: 5 mg/day, except for postmenopausal women not receiving estrogen, who should receive 10 mg/day	Usually minimal: GI symptoms, altered taste, nighttime leg cramps. Rarely: acute-phase reactions involving fever and lymphopenia, joint or muscle pain, skin reactions, ocular effects. Esophageal ulceration is a rare side effect of aminobisphosphonates; patient must take with a full glass of water and not lie down for 30 min after taking. Safety in impaired renal function (ClCr <35 mL/min) is unknown.	Must be taken at least 30 min before the first food, beverage or medication with a full glass of plain water only. Do not lie down for 30 min after taking the dose. Ensure recommended intake of calcium and vitamin D (from diet and/or supplements). Retrospective analysis suggests alendronate prevents fractures within the first year of therapy. ONJ has been reported in cancer patients on high-dose iv bisphosphonates and rarely with oral doses used for OP. Although available evidence does not prove a causal link, advise patients to complete elective dental work if possible before starting oral bisphosphonates. Atypical fractures of the femur: Although extremely rare, they may be more common among those undergoing long-term bisphosphonate therapy; however, a link has not been definitely established. Radiography or bone scanning (or both) should be considered for individuals who have been on long-term bisphosphonate therapy and who experience new thigh pain.[3]
risedronate Actonel, generics	Prevention of OP in postmenopausal women: 5 mg/day or 35 mg/wk Treatment of OP in postmenopausal women: 5 mg/day; 35 mg once weekly; or 150 mg once per month Treatment & prevention of glucocorticoid-induced OP (men & women): 5 mg/day Treatment of OP in men (to improve BMD): 35 mg once weekly	See alendronate. Safety in impaired renal function (ClCr <35 mL/min) is unknown.	See alendronate. Risedronate has been shown to prevent fractures within the first year of therapy.
Oral bisphosphonate/nutritional supplement combinations			
alendronate/ vitamin D Fosavance	Treatment of OP in postmenopausal women & men: alendronate 70 mg plus vitamin D_3 2800 IU or 5600 IU once weekly	See alendronate.	See alendronate.

Drug	Dose	Adverse effects	Comments
etidronate/ calcium Didrocal, generics	Cyclic: 400 mg/day × 14 days then calcium 500 mg (as carbonate) on days 15–90. Repeat.	Side effects are usually minimal: GI symptoms, altered taste, nighttime leg cramps. Very rarely reported: acute-phase reactions involving fever and lymphopenia, joint or muscle pain, skin reactions, ocular effects. Safety in impaired renal function (ClCr <35 mL/min) is unknown.	Etidronate should be taken on an empty stomach with a full glass of water. To aid compliance, it is recommended that patients take the therapy at bedtime, at least 2 h before or after eating. Calcium supplements should be separated by at least 2 h before or after.
Intravenous bisphosphonates			
zoledronic acid Aclasta	Treatment of OP in postmenopausal women (to ↓ incidence of fractures) & men (to ↑ BMD); treatment & prevention of glucocorticoid-induced OP: 5 mg once yearly iv; infuse over 15–30 min Prevention of postmenopausal OP in women with osteopenia: 5 mg as a single iv infusion	In rare instances, deterioration of renal function may occur following administration. To minimize risk, do not use in patients with ClCr <30 mL/min. 10–20% of patients experience acute-phase reaction 24–72 h after infusion, lasting up to 3–4 d; fever and lymphopenia, joint or muscle pain, skin reactions, ocular effects. Rare: atrial fibrillation.	Product is packaged as 5 mg/100 mL ready-to-use infusion. Patients should be well hydrated (500 mL of water) prior to and following administration. ONJ has been reported in cancer patients on high-dose iv bisphosphonates and rarely with oral doses used for OP. Although available evidence does not prove a causal link, advise patients to complete elective dental work if possible before starting oral bisphosphonates.
RANK ligand inhibitors			
denosumab Prolia	Treatment of postmenopausal women with OP at high risk for fracture or who have failed or are intolerant to other available therapy: 60 mg once every 6 mo sc	Eczema, rarely serious infections, cellulitis. Hypocalcemia in patients with reduced GFR or vitamin D insufficiency. Dose adjustment is not necessary with renal impairment.	Ensure recommended intake of calcium and vitamin D (from diet and/or supplements). Keep refrigerated. ONJ has been reported in trials using high doses (120 mg every month) in oncology patients. A dental exam should be considered prior to treatment in patients at risk.
Selective estrogen receptor modulators			
raloxifene Evista, generics	Treatment and prevention of OP in postmenopausal women: 60 mg/day	Leg cramps, hot flashes especially in younger postmenopausal women. Venous thromboembolism risk similar to estrogen.	Ensure recommended intake of calcium and vitamin D (from diet and/or supplements). May aggravate hot flashes; should not be started until postmenopausal status is confirmed.
Hormone therapy: estrogens, oral			
*conjugated estrogen** Premarin	0.3–1.25 mg po daily	Bloating, headache, nausea, breast tenderness, dose-related bleeding. For most women in their early postmenopausal years, short-term use (<5 yrs) of hormone therapy will *not* translate into an ↑ risk of cardiovascular disease or breast cancer. Any ↑ risk of breast cancer from longer-term use is similar to that from lifestyle factors.[4]	For postmenopausal women requiring treatment of OP in combination with treatment for vasomotor symptoms, hormone therapy can be used as first-line therapy for prevention of hip, nonvertebral and vertebral fractures. Also indicated for prevention of OP in women experiencing early menopause (before age 45).
conjugated estrogen sulfate† CES, generics	0.3–1.25 mg po daily	See above.	See above.
17β-estradiol micronized Estrace	0.5–2 mg po daily	See above.	See above.
Hormone therapy: estrogens, transdermal			
17β-estradiol, patch Climara, Estraderm, Estradot, generics	Climara: 1 patch applied weekly Estraderm, etc.: 1 patch 2x/wk	Bloating, headache, nausea, breast tenderness, dose-related bleeding, redness, skin irritation.	Estraderm is a reservoir patch; others are matrix patches.

Drug	Dose	Adverse effects	Comments
Calcitonin peptides			
calcitonin salmon, intranasal Miacalcin NS, generics	200 IU/day intranasally	Local effects such as rhinitis, nasal dryness with crusting, nonsevere epistaxis and sinusitis. Rarely associated with systemic effects such as nausea, vomiting, dizziness, flushing accompanied by a sensation of heat and, uncommonly, polyuria and chills.	Indicated for women >5 yrs postmenopausal. Has been shown to prevent vertebral fractures and reduce pain associated with acute vertebral fractures. Recommended for women intolerant of first-line therapies for prevention of vertebral fractures.[3]
Anabolic agents			
teriparatide Forteo	Treatment of severe OP in postmenopausal women at high risk of fracture or who have failed or are intolerant to previous therapy; treatment of OP associated with sustained systemic glucocorticoid therapy in men & women who are at increased risk for fracture; to increase bone mass in men with primary or hypogonadal severe OP who have failed or are intolerant to previous therapy: 20 μg/day sc for 24 months (lifetime exposure)	Nausea, dizziness, leg cramps. Not to be prescribed to patients with an increased baseline risk of osteosarcoma. Patients should be in a supine or sitting position for administration because of the rare risk of orthostatic hypotension.	Limited data available concerning use in renal or hepatic impairment. 2010 guidelines also indicate this drug may decrease pain associated with vertebral fractures.[3]

* Conjugated estrogen contains a mixture of estrone, equilin, 17α-dihydroequilin, 17α-estradiol, 17β-dihydroequilin, δ8,9-dehydroestrone, 17β-estradiol, equilenin, 17α-dihydroequilenin, 17β-dihydroequilenin as salts of their sulfate esters.
† Conjugated estrogen sulfate contains estrone, equilin, 17α-dihydroequilin, 17α-estradiol, equilenin and 17α-dihydroequilenin as salts of their sulfate esters.
Abbreviations: BMD = bone mineral density; CrCl = creatinine clearance; GFR = glomerular filtration rate; GI = gastrointestinal; iv = intravenous; ONJ = osteonecrosis of the jaw; OP = osteoporosis; po = by mouth; sc = subcutaneous.

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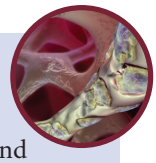

Practice tips[1-4]

- Alendronate, risedronate, zoledronic acid, denosumab, estrogen and teriparatide are all considered first-line agents for patients with established osteoporosis. Raloxifene is also a first-line therapy for postmenopausal women for prevention of vertebral fractures.
- A bisphosphonate (alendronate, risedronate or zoledronic acid) or teriparatide is the preferred therapy for the prevention and treatment of glucocorticoid-induced osteoporosis.
- Bisphosphonates, although widely used for osteoporosis treatment, have very poor intestinal absorption after oral administration. Strict observance of dosing instructions is essential, although difficult, and often leads to adherence problems (*see Adherence, page S21*). An intravenous bisphosphonate (zoledronic acid) can be used to overcome adherence issues, occasional gastrointestinal adverse effects or lack of response to oral agents.
- Teriparatide therapy is limited to 24 months' lifetime exposure. It is recommended to treat with a bisphosphonate or other antiresorptive agent after anabolic agent is completed, to preserve gains made with this therapy.
- Denosumab is a human monoclonal antibody and the first biologic agent approved for the treatment of osteoporosis in Canada. Its injectable administration every 6 months may make it an alternative to those who have difficulty with oral therapies. It may also be useful for patients with renal insufficiency, as it is not cleared by the kidneys.
- Adequate calcium and vitamin D intake is essential for all patients receiving pharmacologic therapy for osteoporosis.

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