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Osteoporosis: A quick update

This review of the latest recommendations regarding screening and Tx regimens can help you refine your approach and reduce patients' risk of fractures.

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PRACTICE RECOMMENDATIONS

› *Use bisphosphonates (except ibandronate) and denosumab as first-line pharmacologic treatment for osteoporosis.* (A)

› *Treat patients for 5 years with oral bisphosphonates and 3 years with intravenous bisphosphonates before reviewing therapy, unless there are complications.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Researchers estimate that approximately 10.2 million Americans have osteoporosis, and an additional 43 million have low bone density.[1] Equally stark are the ramifications of these numbers. About one out of every 2 Caucasian women will experience an osteoporosis-related fracture at some point in their lifetime, as will approximately one in 5 men.[2] Although African American women tend to have a higher bone mineral density (BMD) than white women throughout their lives, those who have osteoporosis have the same elevated risk for fractures as Caucasians.

Osteoporotic fractures are associated with increased risk of disability, mortality, and nursing home placement. Given the aging population, researchers expect annual direct costs from osteoporosis to reach $25.3 billion by 2025.[3]

Family physicians (FPs) can have a meaningful impact on the extent to which this condition affects the population. To that end, we've put together a brief summary of the screening recommendations to keep in mind and a comparison of the different agents used to treat and prevent osteoporosis. The reference tables throughout will put these details at your fingertips.

Screening recommendations vary, Dx doesn't require BMD testing

Guidelines for screening for osteoporosis vary considerably by professional organization. For example, the US Preventive Services Task Force (USPSTF) recommends screening all women ≥65 years, and younger women whose fracture risk is the same, or greater than, that of a 65-year-old white woman who has no additional risk factors (**TABLE 1**[4]).[5] In addition, the USPSTF concludes that the current evidence is insufficient to recommend routine screening for osteoporosis in men.[5]

The National Osteoporosis Foundation (NOF) recommends that BMD testing be performed in all women ≥65 years and in men ≥70 years.[6] In terms of frequency, NOF recommends BMD testing one to 2 years after initiating therapy to reduce fracture risk and every 2 years thereafter. The American

TABLE 1

Clinical risk factors used for the assessment of osteoporosis[4]

Primary causes of osteoporosis include:
• Increasing age
• Female sex
• Low body weight (<128 pounds)
• Previous fragility fracture, particularly of the hip, wrist, and spine, and including morphometric vertebral fracture
• Parental history of hip fracture
• Glucocorticoid treatment (by mouth for ≥3 months)
• Current smoker
• Alcohol intake of ≥3 drinks daily
Secondary causes of osteoporosis include:
• Rheumatoid arthritis
• Untreated hypogonadism in men and women
• Inflammatory bowel disease
• Prolonged immobility
• Organ transplantation
• Type I diabetes
• Thyroid disorders
• Chronic obstructive pulmonary disease

Adapted from: Kanis JA, et al. *Osteoporos Int*. 2013.[4]

Bone mineral density testing is not always necessary to establish a diagnosis of osteoporosis.

College of Obstetricians and Gynecologists recommends BMD screening for women no more than every 2 years starting at age 65 years.[7] It also recommends selective screening in women younger than 65 years of age if they are postmenopausal and have other risk factors for osteoporosis.[7]

The most recent guideline regarding osteoporosis was published in May 2017 by the American College of Physicians (ACP) and endorsed by the American Academy of Family Physicians.[8] But the guideline focuses on treatment rather than screening.

Although guidelines vary by society, most experts agree with BMD assessment in all women ≥65 years and postmenopausal women <65 years if one or more of the risk factors identified in **TABLE 1**[4] are present.

Diagnosis. Osteoporosis can be diagnosed using dual energy x-ray absorptiometry (DXA) and T-score (**TABLE 2**[6]),[9] but BMD testing is not always necessary to establish the diagnosis. For example, osteoporosis can be diagnosed clinically in both men and women who have sustained a hip fracture (with or without BMD testing). Osteoporosis may also be diagnosed in patients with osteopenia (determined by DXA and T-score) who have had a vertebral, proximal humeral, or pelvic fracture. Generally speaking, a detailed history and physical together with BMD assessment, vertebral imaging to diagnose vertebral fractures, and, when appropriate, the World Health Organization's 10-year estimated fracture probability, are all utilized to establish patients' fracture risk.[6,10]

Treatment: Which agents and for how long?

Once a patient is diagnosed with osteoporosis, answering the following questions will help with selection of the best therapy for the patient:

1. Where on the body is BMD the lowest (vertebral, nonvertebral, or hip)

TABLE 2

National Osteoporosis Foundation diagnostic classifications[6]

Classification	T-score
Normal	-1.0 and above
Osteopenia	Between -1.0 and -2.5
Osteoporosis	At or below -2.5
Severe or established osteoporosis	-2.5 or lower + fragility fracture

Adapted from: Cosman F, et al. *Osteoporos Int*. 2014.[6]

and, consequently, at highest risk for a fracture?

2. Does the patient have any conditions that would interfere with therapy (difficulty swallowing, esophageal/gastrointestinal irritation)? This is important, as certain agents are associated with severe esophagitis.
3. Does the patient have any issues that would prevent adherence? Adherence may improve with therapy that is administered less frequently (weekly, monthly, once every 3 months, or annually).

TABLE 3[6,11-14] lists the prescription medications used to treat and prevent osteoporosis, their effect on the risk of vertebral, hip, and nonvertebral fractures, and contraindications/major adverse effects. First-line therapies are recommended based on clinical trials comparing the medication to placebo and evaluating their effectiveness in lowering the risk of vertebral, hip, and nonvertebral fractures.[15] Given the absence of studies comparing these drugs to one another, **TABLE 3**[6,11-14] should not be used to make direct comparisons.

A new monoclonal antibody, romosozumab, has shown statistically significant decreases in the risk of new vertebral and nonvertebral fractures compared to alendronate after 12 months of use.[16] However, there was a statistically significant higher number of patients who had a cardiac ischemic event or revascularization while taking romosozumab compared with those taking alendronate in the one-year double-blind period of the study.[16] As of press time, the US Food and Drug Administration has not approved romosozumab.

Duration of treatment should be individualized based on specific patient factors, the pharmacologic agent, and, of course, adverse effects. However, no pharmacologic agent should be used indefinitely.[6] In its clinical practice guidelines, the ACP recommends that patients be treated for 5 years with an appropriate pharmacologic therapy.[8] The American Society for Bone and Mineral Research (ASBMR) Task Force recommends a review of therapy after 3 years with an intravenous bisphosphonate (BP; strength of recommendation [SOR]=C).[17]

A review of 2 recent long-term trials analyzing the effects of BPs offers some additional guidance regarding duration of therapy in Caucasian postmenopausal women.[18] In one study, women who received 10 years of therapy with alendronate reported fewer vertebral fractures than those who were switched to placebo after 5 years of treatment.[19]

In the second trial, which studied zoledronic acid, there were fewer morphometric vertebral fractures for those participants given annual injections for 6 years vs 3 years.[20] This trial found a significant transient increase in serum creatinine >0.5 mg/dL in the zoledronic acid treatment group.

These findings have prompted some experts in the field of osteoporosis to call for physicians to consider longer therapy with a

Individualize duration of therapy based on patient factors and the pharmacologic agent being used, but no agent should be used indefinitely.

Strength of recommendation (SOR)

A Good-quality patient-oriented evidence

B Inconsistent or limited-quality patient-oriented evidence

C Consensus, usual practice, opinion, disease-oriented evidence, case series

TABLE 3

Medications for the prevention and treatment of osteoporosis[6,11-14]

Effect on bone/-class	Medication	Dose	Vertebral fracture risk*	Hip fracture risk*	Nonvertebral fracture risk*	Comments
First-line treatments						
Antiresorptive/-bisphosphonate	Alendronate (Fosamax, Binosto)	*Treatment*: 10 mg/d PO or 70 mg/wk PO *Prevention*: 5 mg/d PO or 35 mg/wk PO	↓40%-64% Most studies used 10 mg/d tablets	↓21%-55% Most studies used 10 mg/d tablets	↓11%-49% Most studies used 10 mg/d tablets	*Contraindications*: Abnormalities of the esophagus; hypocalcemia; increased risk of aspiration or dysphagia with effervescent tablets or oral solution *Major adverse effects*: GI/esophageal irritation; risk of atypical femur fracture; risk of osteonecrosis of the jaw (0.03%-4.3%) Patients must be able to stand or sit upright for at least 30 minutes
Antiresorptive/-bisphosphonate	Risedronate (Actonel, Atelvia)	*Treatment or prevention (immediate release)*: 5 mg/d or 35 mg/wk or 150 mg/mo *Treatment with delayed release*: 35 mg/wk	↓46%-69%	↓36%-40%	↓19%-60%	*Contraindications*: Abnormalities of the esophagus; hypocalcemia *Major adverse effects*: GI/esophageal irritation; risk of atypical femur fracture; risk of osteonecrosis of the jaw (0.03%-4.3%) Patients must be able to stand or sit upright for at least 30 minutes
Antiresorptive/-bisphosphonate	Zoledronic acid (Reclast)	*Treatment*: 5-mg IV infusion/yr *Prevention*: 5-mg IV infusion every 2 yrs	↓66%-77%	↓44%	↓27%-28%	*Contraindications*: Hypocalcemia *Major adverse effects*: Risk of atypical femur fracture (subtrochanteric fracture 2-100 per 100,000 women); risk of osteonecrosis of the jaw (0.03%-4.3%) Patients must be appropriately hydrated prior to treatment
Antiresorptive/-RANKL inhibitor	Denosumab (Prolia)	*Treatment*: 60 mg subQ as a single dose once every 6 mos	↓60%	↓41%	↓20%	*Contraindications*: Hypocalcemia; pregnancy
Alternate treatments						
Anabolic/-recombinant human parathyroid hormone	Teriparatide (Forteo)	*Treatment*: 20 mcg subQ once daily for up to 2 yrs	↓64%-69%	No difference	↓35%-40%	*Major adverse effects*: Orthostatic hypotension; may exacerbate urolithiasis; increases risk for osteosarcoma Initial administration should occur when patient is sitting or lying down
Antiresorptive/-bisphosphonate	Ibandronate (Boniva)	*Treatment*: 150 mg/mo PO or 3 mg IV quarterly *Prevention*: 150 mg/mo PO	↓51%	No difference (data for fracture not separated in studies)	No difference	*Contraindications*: Abnormalities of the esophagus; hypocalcemia *Major adverse effects*: GI/esophageal irritation; risk of atypical femur fracture; risk of osteonecrosis of the jaw (0.03%-4.3%) Patients must be able to stand or sit upright for at least 30 minutes

*Reductions in fractures are relative risk reduction percentages pooled from trials with drug vs placebo in trials involving postmenopausal women and should not be used to directly compare agents in a class.

CONTINUED

TABLE 3

Medications for the prevention and treatment of osteoporosis[6,11-14] *continued*

Effect on bone/-class	Medication	Dose	Vertebral fracture risk*	Hip fracture risk*	Nonvertebral fracture risk*	Comments
Antiresorptive/-estrogen agonist/-antagonist	Raloxifene (Evista)†	*Treatment*: 60 mg/d	↓34%-44%	No difference	No difference	*Contraindications*: History of or current venous thromboembolic disease (discontinue at least 72 hours prior to, and during, prolonged immobilization); pregnancy or breastfeeding Increased risk of death in postmenopausal women with documented coronary heart disease or increased risk for major coronary reactions FDA approved for risk reduction for invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women with high risk for invasive breast cancer
Last-line treatments						
Antiresorptive/-tissue-selective estrogen complex or 3rd-generation selective estrogen receptor modulator	Bazedoxifene 20 mg with conjugated equine estrogens 0.45 mg (Duavee)†	*Prevention only*: 1 tab/d	No data	No data	No data	*Contraindications*: Undiagnosed or abnormal uterine bleeding; active, past history of, or increased risk of, venous thromboembolism or arterial thromboembolic disease; carcinoma of the breast; estrogen-dependent tumors; hepatic impairment or disease; pregnancy or breastfeeding; history of angioedema; anaphylaxis to any of the components
Antiresorptive/-calcitonin	Calcitonin (subQ or IM injection [Miacalcin]; intranasal formulations are available only as generics)	*Treatment*: Intranasal: 200 units (1 spray) in one nostril once daily IM or subQ 100 units/d	Decreases (studies included intranasal formulation only)	No difference	No difference	*Major adverse effects with nasal spray*: Rhinitis; epistaxis; allergic rhinitis. Possible increase in risk for malignancy; however, causal relationship not established Calcitonin should be used for treatment of osteoporosis in women ≥5 years post-menopause who are unable to take other treatments

BMD, bone mineral density; GI, gastrointestinal; IM, intramuscularly; IV, intravenously; subQ, subcutaneously.

*Reductions in fractures are relative risk reduction percentages pooled from trials with drug vs placebo in trials involving postmenopausal women and should not be used to directly compare agents in a class.

†The American College of Physicians recommends against the use of this drug to treat osteoporosis in women or did not include it in its 2017 guideline.[8]

BP (10 years with oral therapy or 6 years with intravenous therapy) in high-risk postmenopausal women (older women, those with a low hip T-score or high fracture risk score, those with a previous major osteoporotic fracture, and those who experienced fracture while on therapy) (SOR=B).[18]

Two rare adverse effects to keep in mind

The incidence of atypical femoral fracture, although rare (2-100 per 100,000 women), increases with duration of BP use. As a result, a drug holiday of 2 to 3 years should be considered for women with a low risk

for fracture after 3 to 5 years of BP therapy (SOR=C).[18]

Osteonecrosis of the jaw (ONJ), also known as antiresorptive-associated osteonecrosis of the jaw, is a rare adverse effect of BPs that is associated with higher drug potency, higher cumulative dose, and parenteral route of administration, as well as other risk factors.[17,21] The American Association of Maxillofacial Surgeons (AAOMS) states that the risk of developing ONJ increases with use of oral BPs for more than 4 years;[22] however, the Task Force of the ASBMR states that the evidence to support this is of poor quality.[18] No recommendations on duration of therapy based on risk for ONJ have been made; however, AAOMS recommends discontinuation of oral BPs for a period of 2 months prior to, and 3 months following (or until osseous healing has occurred), elective invasive dental surgery for patients who have been taking an oral BP ≥4 years (SOR=C).[22]

If a long-term drug holiday is selected, patients should be reassessed in 2 years. Shorter duration of follow-up is warranted for patients taking denosumab, teriparatide, or raloxifene, since bone loss will resume once therapy is discontinued.[18]

Because the benefits of BPs (in terms of reducing the risk of vertebral fracture) are significantly greater than the risks of an atypical fracture or ONJ, therapy should be started in appropriate patients, but duration of therapy should be monitored closely. JFP

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Review therapy after 5 years with an oral bisphosphonate and after 3 years with an intravenous one.