Evaluation and Treatment of Osteoporosis

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KEYWORDS

• Osteoporosis • Postmenopausal women • Men • Screening • Diagnosis
• Treatment

KEY POINTS

- Screening for osteoporosis is recommend in all women more than 65 years of age or in women aged 50 to 64 years with certain risk factors.
- Treatment should be considered in postmenopausal women with osteoporosis on dual-energy x-ray absorptiometry scan, history of fragility fracture, or osteopenia plus a FRAX (Fracture Risk Assessment Tool) score of greater than or equal to 3% at the hip or greater than or equal to 20% at other sites.
- All of the osteoporosis agents decrease the risk of vertebral fractures but only some bisphosphonates, denosumab, and estrogen decrease hip fracture risk.
- Make sure the medication chosen to treat osteoporosis decreases fracture risk at the site of decreased bone mineral density or fracture. Also consider side effects, contraindications, secondary benefits, cost, and likelihood of adherence.
- Bisphosphonates should be first-line therapy in most cases.

INTRODUCTION

As the population ages, osteoporosis-related and osteoporosis-related fractures pose a significant public health concern. Although there has been a recent decline in hip fracture incidence in white women and men in the United States, rates are holding fairly steady in black, Asian, and Hispanic men and women.[1] Because of the aging of the population, fracture rates are expected to increase by 48% in the United States over the next 25 years to greater than 3 million fractures associated with a cost of $25.3 billion.[2] Seventy-one percent of all fractures and 75% of all fracture-related costs occur in women.[2] Approximately 20% of patients with a hip fracture do not survive for more than a year from diagnosis and more than 50% never completely regain

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their prefunction status.[3] Knowing these risks, the aim is for appropriate diagnosis and treatment of osteoporosis. The focus of this article is on the pharmacologic management of osteoporosis in postmenopausal women. It is important to recognize that nonpharmacologic interventions such as exercise, smoking cessation, fall prevention, and avoidance of heavy alcohol use are also recommended in the treatment of osteoporosis but these are not addressed in this article.

WHOM TO SCREEN

Most expert groups recommend screening with dual-energy x-ray absorptiometry (DXA) scan in postmenopausal women at age 65 years or older regardless of risk factors. For postmenopausal women between the ages of 50 and 64 years, differing screening recommendations exist. Organizations such as the National Osteoporosis Foundation (NOF), Endocrine Society, and Canadian Osteoporosis Society recommend screening in this age group when risk factors are present. Risk factors include advanced age, previous fracture, long-term glucocorticoid use, low body weight (less than 58 kg [127 lb]), family history of hip fracture, tobacco use, or excess alcohol use, with the most robust risk factors being age and previous low-trauma fracture[4] (**Box 1**). The United States Preventive Services Task Force (USPSTF) proposed the use of the FRAX calculator (https://www.shef.ac.uk/FRAX/) to determine need for screening in women aged 50 to 64 years.[5] If the FRAX 10-year major osteoporotic risk is greater than or equal to 9.3%, which is equivalent to a 65-year-old white woman without risk factors, then the USPSTF recommends screening with dual-energy x-ray absorptiometry (DXA) scan.[6] There are other, less complicated, screening tools, such as the Osteoporosis Risk Assessment Instrument (ORAI), Osteoporosis Self-assessment Tool (OST), Osteoporosis Index of Risk (OSIRIS), and Simple Calculated Risk Estimation Score (SCORE), which performed equally to FRAX in predicting fracture in comparison studies[7,8] (**Table 1**).

There are limited data to guide recommendations regarding rescreening if initial testing does not reveal osteoporosis. Most expert groups recommend rescreening in 1 to 2 years if women are at high risk for accelerated bone loss. In 2012, a prospective cohort study of almost 5000 women estimated the time interval for 10% of these women to develop osteoporosis before having a clinical hip or vertebral fracture. Based on this study the following rescreening recommendations can be considered. If baseline T score is −2.00 to −2.49 (advanced osteopenia) or if risk factors are present for accelerated bone loss regardless of T score, then repeat DXA every 2 years. If baseline T score is −1.50 to −1.99 (moderate osteopenia) with no risk factors for

Box 1
Risk factors for osteoporosis

- Advanced age
- Previous low-trauma fracture
- Long-term glucocorticoid use
- Low body weight (<58 kg [127 lb])
- Family history of hip fracture
- Tobacco use
- Excess alcohol use

Table 1
Screening recommendations

Population	DXA Scan Screening Recommendations
Postmenopausal women aged ≥65 y	Screen regardless of risk factors
Postmenopausal women aged 50–64 y	• Screen if 1 or more risk factor present ○ National Osteoporosis Foundation (NOF) ○ Endocrine Society ○ Canadian Osteoporosis Society • Screen if FRAX 10-y major osteoporotic fracture risk ≥9.3% ○ USPSTF • Additional screening calculators ○ ORAI ○ OST ○ OSIRIS ○ SCORE
Men aged >70 y	• Insufficient evidence to screen ○ USPSTF • Screen regardless of risk factors ○ NOF ○ Endocrine Society ○ International Society for Clinical Densitometry
Men aged 50–70 y	• Insufficient evidence to screen ○ USPSTF • Screen if 1 or more risk factors present ○ NOF ○ Endocrine Society ○ International Society for Clinical Densitometry

Abbreviations: ORAI, Osteoporosis RIsk Assessment Instrument; OSIRIS, Osteoporosis Index of Risk; OST, Osteoporosis Self-assessment Tool; SCORE, Simple Calculated Risk Estimation Score; USPSTF, US Preventive Services Task Force.

accelerated bone loss, then repeat DXA in 3 to 5 years. If baseline bone mineral density (BMD) is normal or T score is −1.01 to −1.49 (mild osteopenia) with no risk factors for accelerated bone loss, then consider repeating the DXA in 10 to 15 years[9] (Table 2).

WHOM TO TREAT

Osteoporosis can be diagnosed based on BMD or the history of a fragility fracture. A fragility fracture is defined as a fracture occurring in the absence of major trauma such as a fall from standing height, coughing, or sneezing. The most common sites for fragility fracture involve the spine, ribs, hip, pelvis, wrist, or humerus. Based on DXA scan measurements, osteoporosis is defined as spinal or hip BMD 2.5 standard deviations or more less than the mean for healthy young women (T score −2.5 or less). Osteopenia is defined a spinal or hip BMD between 1 and 2.4 standard deviations less than the mean (T score −1.0 to −2.4) (Table 3). Based on NOF recommendations, treatment should be considered in postmenopausal women with a history of hip or vertebral fracture or with osteoporosis on BMD measurements (T ≤ −2.5). In addition, it has been deemed cost-effective to consider treatment in postmenopausal women with osteopenia (T score between −1.0 and −2.4) if their 10-year probability of hip fracture reaches 3% or if major osteoporotic fracture (hip, shoulder, or wrist) risk is

Table 2
Rescreening recommendations

Baseline Screening DXA Results	Follow-up Plan
Normal	Consider recheck DXA in 10–15 y
Mild osteopenia, T −1.01 to −1.49	Consider recheck DXA in 10–15 y
Moderate osteopenia, T −1.5 to −1.99	Consider recheck DXA in 5 y
Advanced osteopenia, T −2.0 to −2.49 or if risk factors for accelerated bone loss regardless of baseline T score	Consider recheck DXA in 1–2 y
Osteoporosis	Discuss work-up ± treatment

greater than or equal to 20% based on the FRAX calculator.[10] Although it may be cost-effective, clinical trials have not assessed the benefit on absolute fracture risk using these FRAX-based treatment criteria (**Box 2**).

Cost-effectiveness analysis was based on the use of generic bisphosphonates for treatment of osteoporosis.[10] Additional studies are needed to determine at what level of risk it will remain cost-effective when the more expensive, newer agents are used. Clearly the emphasis on treatment in women with high absolute fracture risk rather than BMD criteria alone will increase the number of women treated. In a prospective cohort of community-dwelling white women greater than or equal to 65 years of age, recommendations for pharmacotherapy occurred for 72% of women more than 65 years old and 93% of women more than 75 years old when the revised NOF treatment guidelines were used.[11] When considering BMD criteria alone, only 50% of women in both age groups were recommended treatment. Shared decision making between provider and patient based on risks and benefits is needed to decide whether treatment is appropriate.

HOW TO CHOOSE A TREATMENT

Most medications available to treat osteoporosis are antiresorptives, which slow bone turnover by decreasing resorption. These antiresorptives include the bisphosphonates, selective estrogen receptor modulators (SERMs), denosumab, estrogen, and calcitonin. The only anabolic agent that stimulates bone formation is teriparatide. There are few head-to-head drug comparison trials to help determine efficacy.[12] Consequently, choice of drug should be based on site of diminished BMD and/or fracture, any secondary benefits, and contraindications. In the absence of contraindications, a generic oral bisphosphonate is recommended as first-line therapy because of low cost and availability of long-term safety data.

Table 3
Interpretation of DXA results

T Score	Interpretation
T +0.9 to −0.9	Normal
T −1.0 to −2.4	Osteopenia
T −2.5 or less	Osteoporosis
T −2.5 or less + fragility fracture	Severe osteoporosis

Box 2
When to consider treatment of osteoporosis

- Osteoporosis based on DXA measurements of BMD
- History of hip or vertebral fracture
- Osteopenia on DXA scan + 10-year FRAX score of greater than or equal to 3% at hip or greater than or equal to 20% of major osteoporotic fracture

It is important to recognize that not all agents prevent fracture at all sites. Adequate data support vertebral fracture reduction with all the medications; however, at this time, data only support hip fracture reduction with most of the bisphosphonates, denosumab, and estrogen[13] (**Tables 4** and **5**).

CALCIUM AND VITAMIN D SUPPLEMENTATION

Controversy exists around the use of calcium and vitamin D supplementation for the prevention of osteoporosis because of the potential increased risks of cardiovascular outcomes and the small increased risk of kidney stones from supplemental calcium use. In 2015, with regard to primary prevention of osteoporosis, the USPSTF stated that there was insufficient evidence for higher-dose calcium (>1000 mg) and vitamin D supplementation in noninstitutionalized postmenopausal women, premenopausal women, and men. They recommended against low-dose (<1000 mg) supplementation in these same populations.[14] With regard to secondary prevention, there are some data that calcium plus vitamin D, but not vitamin D alone, decreases fractures in osteoporotic patients. Target calcium intake for patients with osteoporosis is 1200 mg/d, ideally through diet and 800 IU of vitamin D.[15,16] In order to increase calcium absorption, encourage patients to take their supplements with food and to take them in divided doses if using greater than 500 mg/d. Because calcium supplements can interfere with bisphosphonate absorption, make sure they are taken at least 1 hour after taking oral bisphosphonates. In general, calcium carbonate is recommended because of low cost. If patients are taking an H2 blocker or proton pump inhibitor, or plan to take the supplements on an empty stomach, they should use calcium citrate because an acidic environment is needed for absorption. It is important to make sure that vitamin D levels are replete before starting treatment because there is evidence that efficacy of bisphosphonate therapy is improved considerably in patients with serum 25-hydroxyvitamin D (25-OH) levels of greater than 33 ng/mL.

BISPHOSPHONATES

Bisphosphonates work by slowing bone turnover and they prevent fractures at all sites. The oral bisphosphonates alendronate and risedronate decrease the risk of vertebral and hip fractures by approximately 50% and nonvertebral fractures by 30%. Intravenous (IV) zoledronate reduces the risk of vertebral fractures by 70%, hip fractures by 40%, and nonvertebral fractures by 30%. Oral and IV ibandronate decrease vertebral fracture risk by 50% but there are insufficient data to support hip fracture and nonvertebral fracture reduction.[12,13] In general, the generic oral bisphosphonate alendronate is recommended as first-line therapy because of substantial data on fracture reduction and low cost. As mentioned previously, it is important that vitamin D levels are replete before starting treatment because there is evidence that bisphosphonates are more effective when 25-OH levels are greater

Table 4
Osteoporosis treatment options

Medication	Vertebral Fracture Risk Reduction (%)	Hip Fracture Risk Reduction (%)	Nonvertebral Fracture Risk Reduction (%)	Risks	Secondary Benefits
Bisphosphonates					
Alendronate, risedronate	50	50	30	GERD, esophagitis, jaw osteonecrosis, atypical femur fracture	—
Ibandronate	50	Not enough data	Not enough data		
Zoledronate	70	40	30		
SERMs					
Raloxifene	40	Not enough data	Not enough data	VTE, stroke	50% risk reduction of estrogen receptor–positive breast cancer in high-risk women with use of raloxifene
Bazedoxefine + CEE	—	—	—	Hot flashes (with raloxifene only)	Decrease in hot flashes and atrophic vaginitis with bazedoxifene + CEE
Teriparatide	70	Not enough data	50	Headaches, myalgias, hypercalcemia, hypercalciuria, hyperuricemia Use caution if history of kidney stones or gout	—
Denosumab	70	40	20	Hypocalcemia, hypercholesterolemia, musculoskeletal pain, cystitis, exacerbation of skin conditions, cellulitis	—
Estrogen	30	30	30	Estrogen + progestin: VTE, stroke, coronary heart disease, breast cancer Estrogen: VTE, stroke	—

Abbreviations: CEE, conjugated equine estrogen; GERD, gastroesophageal reflux disease; VTE, venous thromboembolism.

Table 5
Special populations

Population	Medication Recommendations
High risk for breast cancer	50% risk reduction of ER-positive breast cancer in high-risk patients with use of raloxifene
Hot flashes	Bazedoxefine + CEE
Chronic kidney disease	• If CrCl <35 mL/min ◦ Use denosumab (not renally cleared) ◦ Involve nephrologist/endocrinologist comfortable with CKD-MBD. May be able to use renally dosed bisphosphonates or SERM
Esophageal symptoms	• GERD/esophagitis ◦ Can use oral bisphosphonate if symptoms well controlled. Use H2 blocker rather than PPI for treatment of GERD symptoms ◦ IV zoledronate ◦ SERMs ◦ Teriparatide ◦ Denosumab • Barrett esophagus/esophageal stricture/achalasia ◦ Avoid oral bisphosphonates. Can use IV zoledronate ◦ SERMs ◦ Teriparatide ◦ Denosumab

Abbreviations: CKD-MBD, chronic kidney disease–induced metabolic bone disease; CrCl, creatinine clearance.

than 33 ng/mL.[17] It is recommended that all oral bisphosphonates be administered on an empty stomach 30 minutes before breakfast for the best absorption. Superior bioavailability and suppression of bone turnover was shown in a randomized controlled trial when taken before breakfast rather than at other times of fasting.[18] If patients have significant gastrointestinal side effects or if adherence is an issue then once-yearly IV zoledronate may be a better choice. Of note, only 50% of patients who were prescribed oral bisphosphonates were still taking them by 1 year, therefore it is important to inquire about adherence.[19]

There is concern about side effects of gastroesophageal reflux disease (GERD), esophagitis, and esophageal ulcers; however, if administered properly, these risks are low. In patients with well-controlled GERD it is appropriate to use a bisphosphonate if symptoms do not worsen. If treatment of GERD is needed it is probably better to use H2 blockers rather than proton pump inhibitors (PPIs) because of epidemiologic evidence that long-term, high-dose PPI use may increase fracture risk and that PPIs may blunt the effect of bisphosphonates.[20,21] An expensive, effervescent, dissolvable alendronate tablet is now available that may theoretically decrease gastrointestinal side effects compared with the traditional tablet formulation; however, no comparative studies are available.[19,22] Although data are inadequate to determine whether use of bisphosphonates increases risk of esophageal cancer, the US Food and Drug Administration (FDA) currently recommends against its use in patients with Barrett esophagus.[23]

IV formulations are associated with flulike symptoms and risks of hypocalcemia. Vitamin D stores should be replaced if 25-OH levels are less than 15 ng/mL and calcium replacement doses should be doubled 5 to 7 days before IV therapy. Bisphosphonates should be avoided in patients with a creatinine clearance of less than 35 mL/min.

The HORIZON (Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly) Pivotal Fracture trial raised concern about increased risk of atrial fibrillation in patients treated with IV zoledronate.[24] Several follow-up randomized-control and case-control studies both supported and refuted this concern.[25–27] The data for atrial fibrillation risk are conflicting but risk, if present, is likely small. The decision to treat with bisphosphonates should be weighed against the risk for atrial fibrillation versus osteoporotic fracture in the individual patient.

Rates of osteonecrosis are small, with 1 case per 10,000 to 100,000 person-years of treatment.[28] Risk is highest in patients receiving IV therapy in the setting of active cancer (especially metastatic breast cancer or myeloma) or cancer treatment, glucocorticoid use, poor dentition, and invasive dental procedures. In 2014, the American Association of Oral and Maxillofacial Surgeons updated their position paper on medication-related osteonecrosis of the jaw. Data are still limited but recommendations at this time include postponing initiation of bisphosphonates until after completion of invasive dental treatments. If already on a bisphosphonate, a drug holiday of 2 months before the procedure is recommended for patients who have been on bisphosphonates for longer than 4 years regardless of other risk factors. If patients are at high risk (concomitant corticosteroid or antiangiogenic cancer treatment medications) then consider a drug holiday even if bisphosphonate use is less than 4 years. In most cases the bisphosphonate should not be restarted until osseous healing has occurred.[29]

Bisphosphonate efficacy has been shown with up to 10 years of use. Determining length of therapy with bisphosphonates has become complicated because concerns arose about risk for atypical femur fractures (subtrochanteric or femoral shaft) with prolonged use. Although no direct causal evidence links long-term bisphosphonate use to atypical femur fractures (AFF), several case reports, case series, and cohort analyses show an association between the two. Bisphosphonate use for more than 5 years seems to be associated with an increased relative risk of AFF; however, the absolute risk is low (3.2–100 cases per 100,000 person-years), with the longer the duration, the higher the risk.[30,31]

At the same time, the benefit on typical hip fracture reduction generally outweighs the risk of AFF, especially in high-risk individuals. Although there is no consensus regarding length of therapy, clinicians might evaluate the need for a so-called drug holiday once the patient has been treated for 5 years.[32] At that time, if the patient is considered high risk (T score ≤ -2.5, history of previous hip or spine fracture, ongoing high-dose glucocorticoid use, or FRAX 10-year risk score at hip $\geq$3% or $\geq$20% at other sites) therapy should be continued for another 5 years. If moderate risk (T score now greater than -2.5, no prior hip or spine fracture, or FRAX score 10%–20%) consider a drug holiday. If low risk (does not meet criteria for treatment based on BMD, or FRAX score <10%) discontinue therapy[23] (**Table 6**).

If it is decided to take a drug holiday, there are no data to guide when to reinitiate therapy. A reasonable approach may be to reevaluate BMD via DXA scan every 2 to 3 years and consider restarting therapy if there is a rapid decline in BMD. An alternate approach would be to reevaluate fracture risk using the FRAX score and other risk factors every 2 years. Bone turnover markers may also be reasonable to use but there is no specific recommendation on target values or testing intervals[23] (**Box 3**).

If a patient who has been taking bisphosphonates for more than 3 years complains of a dull or aching pain in the groin or midthigh, plain radiographs are recommended to look for cortical thickening (**Fig. 1**) followed by MRI or bone scintigraphy looking for atypical fractures or stress reactions. A transverse-orientation fracture may also be noted on a plain film. If history or images are concerning, stop the bisphosphonate,

Table 6
Recommendation for drug holiday from bisphosphonates after 5 years of therapy: based on expert opinion

Patient Category	Recommendation
High risk: T score still ≤ -2.5 at hip, previous fracture of hip or spine, ongoing high-dose glucocorticoids	Drug holiday not justified. Continue treatment for at least 5 more years
Moderate risk: T score now > -2.5, no prior hip or spine fracture	Consider drug holiday after 3–5 y of treatment with alendronate, risedronate or zoledronate[a]
Low risk: Did not meet current treatment criteria at time of treatment initiation	Discontinue therapy

[a] No information about ibandronate and drug holidays.

encourage adequate calcium and vitamin D supplementation, and refer to orthopedics urgently.

In a patient untreated for osteoporosis, the development of a fragility fracture should trigger a conversation about the importance of treatment because a history of hip fracture increase the risk of future fracture 3.2 times, especially during the first year after the fracture, and the risk remains increased for at least 5 years.[33] However, there is some concern that bisphosphonate therapy may disrupt bone remodeling and delay fracture repair. So how soon after a hip fracture surgery should a bisphosphonate be started? There is only 1 study of IV zoledronate that addresses this question. According to these results the ideal time to initiate a bisphosphonate after hip fracture in order to decrease rate of recurrent fracture and reduce all-cause mortality is between 2 weeks and 90 days.[34]

SELECTIVE ESTROGEN RECEPTOR MODULATORS

SERMs bind to estrogen receptors and have estrogen agonist and antagonist effects depending on the target organ. Raloxifene has more than 8 years of safety and fracture data and decreases the risk of vertebral fracture by approximately 40%.[13,35,36] There are inadequate data to support fracture reduction at hip and nonvertebral sites. Ideal recipients for raloxifene include women who cannot tolerate bisphosphonates but are not at high risk for venous thromboembolism (VTE) or stroke.[37] Raloxifene is dosed at 60 mg orally per day.

In addition, raloxifene reduces invasive, primarily estrogen receptor (ER)–positive, breast cancer risk by at least 50%.[37] This option may be good in women who are at high risk for breast cancer. In the studies on breast cancer reduction, the following constituted high risk: age greater than 60 years, age greater than 35 years with history of lobular carcinoma in situ, ductal carcinoma in situ or atypical ductal or lobular

Box 3
Monitoring drug holidays: empiric approaches to restarting treatment

- DXA and/or biochemical markers of bone turnover every 2 to 3 years
- Reevaluate risk every 2 to 3 years with FRAX calculator
- Any new fracture

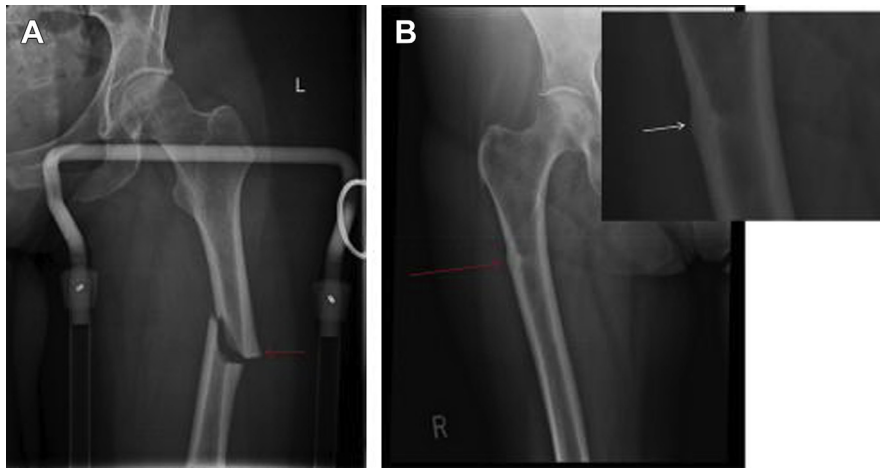

Fig. 1. (*A*) Completed atypical femur fracture. Note the beaking of the lateral cortex (*red arrow*) and short oblique nature of the fracture. There is also minimal comminution noted. (*B*) Incomplete atypical femur fracture. Note the lateral cortex beaking (*red arrow*). Also note the black line that represents the incomplete/nondisplaced fracture of the lateral cortex (*inset, white arrow*). (*From* Tyler W, Bukata S, O'Keefe R. Atypical femur fractures. Clin Geriatr Med 2014;30(2):350; with permission.)

hyperplasia, age 35 to 59 years with Gail model 5-year risk of breast cancer greater than 1.66%, or history of BRCA1 or BRCA2 mutation without prophylactic mastectomy.[38] As opposed to tamoxifen, raloxifene has not shown an increased risk of endometrial cancer so it presents less risk in women with an intact uterus.

Because of its risk of promoting VTE, SERMs should stopped at least 4 weeks before surgeries with moderate to high VTE risks. This recommendation is generally safe when SERMs are being used for the treatment of osteoporosis or breast cancer prevention. If a patient is on a SERM for treatment of breast cancer, then discuss the risks and benefits of stopping it with the patient's oncologist. Ideally, SERMs are restarted several weeks after surgery or when the VTE risk decreases.

One limiting side effect may be hot flashes. A new SERM formulation was recently introduced consisting of bazedoxifene plus conjugated equine estrogen (BZA/CE). Bazedoxifene alone has shown similar fracture reduction rates to raloxifene; however, this formulation is not available in the United States.[39,40] BZA/CE, which is available in the United States, has been shown to improve hot flashes and atrophic vaginitis but fracture and safety data have only been followed for 2 years. In addition, effects on breast cancer risk are unknown.

As opposed to the prolonged duration of action of bisphosphonates on BMD, when SERMs are discontinued BMD loss occurs fairly quickly and is similar to the loss in patients treated with placebo.[41] Consequently, unless side effects or contraindications develop, SERMs should probably be continued long term. Otherwise consider switching to an alternative osteoporosis treatment agent.

TERIPARATIDE

Teriparatide or recombinant human 1-34 parathyroid hormone is the only anabolic agent available for the treatment of osteoporosis. Dosing is a 20-μg subcutaneous injection given in the thigh or abdominal wall daily. It works by activating bone

remodeling rather than slowing bone turnover. It decreases the risk of vertebral fractures by 70% and nonvertebral fractures by 50%; however, data are inadequate to determine hip fracture reduction.[42,43] BMD gains occur in the first few months of treatment; however, it takes at least 6 months before antifracture efficacy occurs.[42] Teriparatide should be stopped after 2 years of treatment because the benefits on BMD begin to level off after 18 months of therapy. In addition, animal studies and 1 human case report showed an increased risk of osteosarcoma with longer-term treatment, although causality between teriparatide and osteosarcoma was not established in the 1 case report.[44,45] Consequently, teriparatide should be avoided in patients at increased risk for osteosarcoma (history of Paget disease, bony radiation, skeletal metastases, and so forth).

Ideal candidates for teriparatide include postmenopausal women with severe vertebral osteoporosis ($T < -3.5$, or $T < -2.5$ plus fragility fracture). Because prior bisphosphonate use may blunt the effect of teriparatide, ideally it should be used first with a plan to transition to an antiresorptive such as a bisphosphonate or SERM after 2 years of treatment.[46] Teriparatide is extremely expensive and can cost up to $2000 per month without insurance. Teriparatide is covered by Medicare part D; however, patients need to show intolerance to or fail bisphosphonate therapy for coverage to be granted in most cases. Treatment with a bisphosphonate or SERM after discontinuation of teriparatide preserves or increases gains in BMD acquired with teriparatide alone. It is unclear how soon after an acute fracture teriparatide should be started because data are limited and conflicting about whether it accelerates or inhibits fracture repair.

Common side effects include headaches, myalgias, nausea, hypercalcemia, and hypercalciuria, so it should be avoided in patients with a history of kidney stones or persistent hypercalciuria. Uric acid levels can also increase and may precipitate a gout attack, therefore avoid the use of teriparatide until uric acid levels are controlled to less than 7.5 mg/dL in patients with a history of gout. Before initiating treatment check serum calcium, phosphate, creatinine, alkaline phosphatase, albumin, 25-OH, uric acid, and 24-hour urine calcium levels. If hypercalcemia or hypercalciuria present, evaluate for primary hyperparathyroidism. Replete vitamin D levels if low before initiating therapy.

DENOSUMAB

Denosumab is a monoclonal antibody that inhibits osteoclast formation and prevents resorption. Similar to bisphosphonates, it decreases fracture risk at all sites. Fracture risk decreases by 70% at the spine, 40% at the hip, and 20% at nonvertebral locations.[47,48] Ideal candidates for denosumab may include osteoporotic postmenopausal women who are intolerant or nonadherent to other medications or those with renal insufficiency (even if creatinine clearance is <35 mL/min). Dosing is 60 mg subcutaneously every 6 months and is only covered by Medicare part B, therefore it should be administered during a clinic visit in Medicare patients.

Most common side effects include musculoskeletal pain, hypercholesterolemia, and cystitis. There is a small increased risk of exacerbating eczema or causing cellulitis that requires hospitalization. Denosumab should be avoided in the setting of hypocalcemia until corrected and any vitamin D deficiency should be corrected before use. In the extension trial of denosumab after eight years of treatment with denosumab in 1546 postmenopausal women, one case of atypical femur fracture and five cases of osteonecrosis of the jaw (ONJ) occurred. There were three cases of ONJ and one atypical fracture in the 1457 cross-over group patients who received five years of

denosumab therapy.[49] Longer-term safety data are needed to learn more about these risks.[49] Data are limited about the effect on acute fracture healing; however, at this time it seems that, even when administered within 6 weeks preceding or following a fracture, there is no delay in healing. There are few data on the idea duration of denosumab therapy or on sequential therapy with other osteoporosis agents. Denosumab has shown efficacy for 8 years.[50] BMD returns to baseline within 2 years after discontinuing therapy.

HORMONE REPLACEMENT THERAPY

Because of potential increased risks of breast cancer, stroke, VTE, and coronary heart disease (CHD), hormone replacement therapy (HRT) is no longer first line for the prevention or treatment of osteoporosis. Data from the Women's Health Initiative (WHI) showed an increase risk of CHD, stroke, VTE, and breast cancer in women on combination estrogen and progestin therapy. In women with hysterectomies who were treated with unopposed estrogen the risk of stroke and VTE was similar to combination therapy but there was no increased risk of CHD and a trend toward slightly lower rates of invasive breast cancer. However, some women who cannot tolerate other osteoporotic agents or who have hot flashes may consider using HRT. The best data for fracture reduction come from the WHI, which showed a 30% to 40% reduction in risk of hip, vertebral, and nonvertebral fractures.[51,52] BMD was not a criterion for randomization into the WHI, therefore baseline BMD may have differed between groups, thus making these results inconclusive. Maximum BMD improvement seems to occur when HRT is started shortly after menopause and continued long-term, but some studies suggest benefit even when started much later in life. Although HRT is not FDA approved for the treatment of osteoporosis, a few small studies have shown fracture reduction in osteoporotic women.[53] It seems that low-dose estrogen (0.3–0.45 mg/d) with or without progesterone is as effective as higher-dose estrogen (0.625 mg/d) in maintaining BMD.[54]

CALCITONIN

The Agency for Healthcare Research and Quality no longer recommends calcitonin for the treatment of osteoporosis because the quality of evidence for fracture reduction is only fair.[55,56] Probably the most beneficial use of calcitonin is for the treatment of acute compression fracture pain. Small studies show a reduction in pain within 4 days of starting the medication for up to 4 weeks of treatment.[57] It is not helpful for treatment of chronic compression fracture pain. Calcitonin, if used for treatment of acute compression fracture pain, is dosed 200 IU alternating nostrils every day or 100 units subcutaneously or intramuscularly every day or every other day. In general, the nasal formulation is recommended because side effects of nausea, vomiting, and flushing are less and analgesia is better compared with the injectable formulations.

STRONTIUM RANELATE

Strontium ranelate is available in Europe for the treatment of osteoporosis. In addition to its antiresorptive effects, strontium accumulates in the bone tissue, therefore the magnitude of BMD changes seen may not be representative of fracture risk reduction. Studies have shown a reduction in vertebral fracture risk by 40% and nonvertebral fracture risk by 15%. In high-risk groups, hip fracture risk may decrease by approximately 40%.[58–61] Strontium ranelate is not available in the Unites States and it is unclear whether the formulations available in the Unites States (citrate, gluconate,

chloride) effectively treat osteoporosis. Side effects and complications, when they occur, can be severe and include diarrhea, VTE, myocardial infarction, drug reaction and eosinophilia and systemic symptoms, Stevens-Johnson, and toxic epidermal necrolysis. It is unclear how long patients should be treated but there are some safety data for up to 10 years.

MONITORING FOR RESPONSE TO THERAPY

There is no consensus on recommended follow-up after initiating treatment of osteoporosis. The controversy arises because it is unclear whether fracture risk reduction correlates with BMD changes while on therapy. Several studies have shown that the greater the improvement in BMD, the greater the fracture reduction.[62–65] However, other studies have suggested that fracture reduction occurs regardless of whether BMD increases or decreases with treatment.[66,67] Most subspecialist societies, including the NOF and the North American Menopause Society, recommend repeating a DXA scan 1 to 2 years after initiating therapy. How often to repeat after that depends on whether improvement or stability in BMD has been achieved or whether the patient is at high risk for more rapid decline of BMD caused by medication side effects or medical conditions. The alternative approach held by the Agency of Health Care Research and Quality is to not repeat a DXA scan after initiating therapy because treatment has been associated with a decreased fracture risk regardless of BMD changes on serial DXAs.[12,55] This option may be reasonable for patients who the clinicians thinks are adherent with medications and are at low risk for rapid decline of BMD caused by malabsorption or glucocorticoid use. If a follow-up DXA is obtained, what the clinician decides to do with the results depends on which philosophy the clinician holds. If BMD is decreasing, assessing for medication adherence and making sure patients are receiving adequate calcium and vitamin D supplementation is a good place to start.

Although in clinical trials bone turnover markers (BTMs) reflect the rate of bone turnover, it is not routinely recommended to check BTMs in patients on antiresorptives because of biological and laboratory variability confounding their use in clinical practice. In addition, there is insufficient evidence to support their use in deciding whether to change therapies based on the results. However, providers may choose to measure BTM in patients with conditions that might interfere with drug absorption or in patients reluctant to take these medications regularly. When using BTMs, measurements should be done at the same time of day in the same laboratory for a given patient in order to decrease risk of variability of results. BTMs cannot be used for patients on the anabolic agent, teriparatide. BTMs include fasting urinary N-telopeptide (NTX) or serum carboxy-terminal collagen cross-links (CTXs). These BTMs can be measured before initiating therapy and then 3 to 6 months later. A decrease in urinary NTX by at least 50% or serum CTX by at least 30% suggests adherence and efficacy. However, a decrease of less than this does not necessarily indicate treatment failure but may trigger the clinician to question the patient about medication adherence or malabsorption. Of note, insurance companies may not cover these tests.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Glucocorticoids exposure, whether endogenous or exogenous, decreases bone density and increases the risk of fracture. Dosages as low at 2.5 to 7.5 mg of prednisone equivalents per day have been associated with increased vertebral and nonvertebral fractures, with higher daily doses likely more harmful.[68] Most BMD loss occurs within the first few months of therapy; however, continued use is associated with a slow and

steady decline. Screening with DXA scan and vitamin D levels are recommended in all patients more than 30 years of age who are anticipated to be on glucocorticoids for greater than or equal to 3 months. These patients should also be encouraged to maintain calcium intake of 1200 mg/d and vitamin D intake of 800 IU/d through diet and/or supplements.

In 2010, the American College of Rheumatology (ACR) published recommendations on evaluation and management of glucocorticoid-induced osteoporosis (GIOP). In nonosteoporotic postmenopausal women and men greater than or equal to 50 years old, the FRAX calculator should be used to determine risk of fracture. In postmenopausal women and men greater than or equal to 50 years old with osteoporosis, history of fragility fracture, or a high-risk FRAX score (hip >3%, major osteoporotic >20%), treatment is recommended for patients on any dose of steroid for any period of time. If they are in the medium-risk category (FRAX score 10%–20% major osteoporotic), consider treatment if steroid use is anticipated for greater than or equal to 3 months. If low risk (FRAX score <10% major osteoporotic), consider treatment if steroids will extend past 3 months with at least 7.5 mg of prednisone equivalents per day. The 2010 ACR article provides a useful algorithm to determine need for treatment.[68] In premenopausal women and men less than 50 years old, treatment should be considered if there is a history of fragility fracture or evidence of accelerated bone loss. There are insufficient data to support treatment in this population if there is no history of fragility fracture (Table 7).

Bisphosphonates (alendronate, risedronate, zoledronate) or teriparatide are recommended for the treatment of GIOP in postmenopausal women, premenopausal women, and men of any age. In general, bisphosphonates are first-line agents because of their substantial data on fracture reduction and low cost. Because of higher cost and subcutaneous route of administration, teriparatide is generally not used as a first-line agent; however, there are some data suggesting that teriparatide

Table 7
Glucocorticoid-Induced Osteoporosis

Risk Categories	Consider Treatment	Which Treatment
Postmenopausal women and men ≥50 y old with osteoporosis, history of fragility fracture, or high-risk FRAX score (>3% hip, >20% major osteoporotic fracture risk)	Any patient on any dose of steroid for any period of time	Bisphosphonates (alendronate, risedronate, zoledronate) or teriparatide
Postmenopausal women and men ≥50 y old with medium-risk FRAX score (10%–20% major osteoporotic fracture risk)	If steroid treatment anticipated for ≥3 mo	Bisphosphonates (alendronate, risedronate, zoledronate) or teriparatide
Postmenopausal women and men ≥50 y old with low-risk FRAX score (<10% major osteoporotic fracture risk)	If steroids will extend past 3 mo with at least 7.5 mg prednisone equivalents per day	Bisphosphonates (alendronate, risedronate, zoledronate) or teriparatide
Premenopausal women and men <50 y old	If there is a history of fragility fracture or evidence of accelerated bone loss	Bisphosphonates (alendronate, risedronate, zoledronate) or teriparatide

leads to greater increases in BMD and lower rates of vertebral fractures compared with alendronate in high-risk patients treated with glucocorticoids.[69–71] Therefore, in patients with severe osteoporosis or those who cannot tolerate or fail other therapies, teriparatide may be the best option (**Box 4**).

TREATMENT OF OSTEOPOROSIS IN MEN

Bone density screening is uncommon in men. Most often DXA scans are obtained after the diagnosis of a low-trauma fracture or after osteopenia was incidentally noted on radiographs. Organizations such as the NOF, Endocrine Society, and International Society for Clinical Densitometry recommend screening all men more than 70 years of age and men between 50 and 70 years of age if certain risk factors are present. Risk factors may include history of fragility fracture, osteopenia on radiograph, loss of more than 37 mm (1.5 inches) of height, long-term glucocorticoid use, human immunodeficiency virus medications, androgen deprivation therapy for the treatment of prostate cancer, hypogonadism, primary hyperparathyroidism, and intestinal disorders. The same T-score classifications are used to diagnoses osteopenia and osteoporosis in men as in women. If osteoporosis is identified, then a work-up for secondary causes should be initiated because there is a high likelihood in men that a secondary cause will be identified. Men should be evaluated for hypogonadism, vitamin D deficiency, renal and liver disease, hyperparathyroidism, celiac disease and other causes of malabsorption, Cushing syndrome, and idiopathic hypercalciuria. Indications for treatment in men more than 50 years of age include osteoporosis on DXA scan, history of fragility fracture, or osteopenia plus high FRAX score (10-year probability of hip fracture $\geq$3% or if major osteoporotic fracture risk is $\geq$20%).[72]

Box 4
Common medications that may decrease BMD or increase fracture risk

- Glucocorticoids
- Antiepileptic drugs: phenobarbital, phenytoin, carbamazepine
- Antiretrovirals for human immunodeficiency virus
- Thiazolidinediones for diabetes
- Sodium-glucose cotransporter-2 inhibitors (canagliflozin) for diabetes
- High-dose medroxyprogesterone acetate for contraception (DepoProvera)
- Aromatase inhibitors
- Gonadotropin-releasing hormone agonists
- Methotrexate
- Cyclosporin and FK506 (tacrolimus)
- Proton Pump Inhibitors
- Lithium
- Antidepressants (selective serotonin reuptake inhibitors and tricyclic antidepressants)
- Loop diuretics
- Heparin (long-term use)
- Excessive thyroid HRT

In general, testosterone replacement therapy is recommended if hypogonadal and there are no contraindications; however, the effect of testosterone therapy on fracture risk has not been evaluated. Treatment options for men include bisphosphonates, teriparatide, and denosumab. All three agents have shown improvement in BMD in men. Only denosumab, when used for treatment of men with nonmetastatic prostate cancer on androgen deprivation therapy, and bisphosphonates have data supporting reduction in fracture risk.[73,74] When choosing between these therapies the same clinical indications, contraindications, and lengths of therapy apply as defined earlier. In general, oral bisphosphonates should be first-line therapy.

SUMMARY

As the population continues to age, the rates of osteoporotic fractures will increase. DXA scan screening is recommended in postmenopausal women more than 65 years of age or women aged 50 to 64 years with risk factors or at high risk of fracture based on FRAX score. DXA should also be considered for all men more than 70 years of age and men between 50 and 70 years of age if certain risk factors are present. Consider treatment if osteoporosis is present, there is a history of fragility fracture, or in the setting of osteopenia plus high risk for fracture based on a FRAX score of greater than or equal to 3% at the hip or greater than or equal to 20% at other sites. All the agents used to treat osteoporosis decrease fracture risk at the spine but only certain bisphosphonates, denosumab, and estrogen have data showing a reduction in hip fracture. The site of diminished BMD or fragility fracture, side effects, contraindications, secondary benefits, cost, and likelihood of adherence should influence the choice of treatment. In most cases, bisphosphonates should be first-line therapy.

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