CME

Osteoporosis in Postmenopausal Women: Considerations in Prevention and Treatment

(Women's Health Series)

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Abstract: Osteoporosis, the most common human bone disease, affects 8 million American women and has significant morbidity and mortality. Screening is important in older women and younger postmenopausal women with additional risk factors for osteoporosis/fracture. Preventive measures include avoiding smoking, excessive alcohol/caffeine intake, and falls in addition to maintaining adequate calcium/vitamin D intake and exercise. Estrogen/hormone therapy may be considered in some patients. Various medications have proven efficacy in treating postmenopausal osteoporosis; however, potential adverse effects such as hypocalcemia, worsening of renal impairment, and osteonecrosis of the jaw must be considered. The optimal duration of therapy requires further investigation.

Key Words: menopause, osteoporosis, prevention, screening, treatment

Osteoporosis, the most common human bone disease,[1] affects 10 million Americans, including 8 million women.[2] Low estrogen levels are a major contributor—20% of bone density is lost within 5 to 7 years of menopause.[2] Fifty percent of women older than 50 years will experience an osteoporosis-related fracture, making risk for hip fracture equal to those of breast, uterine, and ovarian cancers combined.[2] Hip fractures result in 10% to 20% excess mortality within 1 year of the fracture, 20% of patients require care in long-term nursing facilities, and 40% never regain their prefracture level of independence.[1] Mortality also is increased following osteoporotic vertebral fractures.[3] The prevalence of and morbidity/mortality associated with osteoporosis-related fractures underscore the need for healthcare providers to understand the recommendations for screening, diagnosis, prevention, and treatment of postmenopausal osteoporosis.

Screening

Screening recommendations for postmenopausal osteoporosis by the US Preventive Services Task Force,[4] the North American Menopause Society (NAMS),[5] and the National Osteoporosis Foundation (NOF)[5a] are described in Table 1. Although quantitative computerized tomography can be used to assess bone density, dual-energy x-ray absorptiometry (DEXA) of the hip and lumbar spine and quantitative ultrasonography of the calcaneus are the most commonly used screening tests for osteoporosis.[4] Quantitative ultrasonography of the calcaneous is less expensive, more portable, avoids ionizing radiation, and predicts fractures of the femoral neck, hip, and spine, although diagnostic and treatment criteria cite DEXA measurements exclusively.[4] Because bone mineral density (BMD) correlates with bone strength and fracture risk increases exponentially with falling BMD, hip DEXA values (expressed as grams of mineral per square centimeter or T scores that compare the patient's BMD value to "young normal" adults of the same sex, the difference expressed in standard deviations above or below the mean) are the best predictors of future hip fracture risk[3] when measurements are performed by appropriately trained technologists (eg, those certified by the American Registry of Radiologic Technologists or the International Society for Clinical Densitometry) on properly maintained instruments.[3] Two or more

Key Points

- Postmenopausal osteoporosis is an important concept for women's healthcare providers.
- Preventive measures should be instituted in peri- and postmenopausal women.
- Various treatment options are available, but the optimal duration of treatment is not clear.

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Table 1. Comparison of screening recommendations

US Preventive Services Task Force	North American Menopause Society	National Osteoporosis Foundation
Screening by BMD testing for	Screening by BMD testing for	Screening by BMD testing for
All women 65 y old or older	All women aged 65 y old or older	Women aged 65 y old or older
Younger women whose fracture risk is at least that of a 65-year-old white woman with no additional predisposing factors (eg, 10-y risk ≥9.3%, as calculated by the US fracture risk assessment [FRAX] tool [http://www.shef.ac.uk/FRAX/])	Postmenopausal women with either medical causes of bone loss, older than 50 y with additional risk factors (certain fractures after menopause, thinness, parental history of hip fracture, current smoking, rheumatoid arthritis, alcohol intake >2 U/d [eg, 12 oz of beer, 4 oz of wine, or 1 oz of liquor]), or a previous fragility fracture (because of a fall from a standing height)	Younger postmenopausal women and women in menopausal transition with clinical risk factors for fracture
	Screening by vertebral imaging tests (x-ray, lateral vertebral fracture assessment) for	Women who sustain fracture after age 50 y
	Loss of height ≥1.5 in. in a postmenopausal woman	Women with a condition or taking medication associated with low bone mass or bone loss
		Screening by vertebral imaging tests (x-ray, lateral vertebral fracture assessment) for
		Women 70 y old or older
		Women 65–69 y if BMD T score is ≤−1.5
		Postmenopausal women 50–64 y with specific risk factors (low trauma fracture, historical height loss of ≥1.5 in., prospective height loss of ≥0.8 in., recent or ongoing long-term glucocorticoid treatment)

BMD, bone mineral density.

years may be needed between tests to reliably measure a change in BMD because of limitations in testing precision.[4] Repeat DEXA should be performed on the same machine if available because it is not possible to quantitatively compare BMD or calculate least-significant change among machines without cross-calibration.[6]

Various factors, such as patient positioning or osteoarthritis of the spine (which can falsely elevate spine BMD), can affect DEXA results, but studies performed meticulously by experienced certified technologists using appropriately maintained and calibrated equipment should limit such errors. Vertebral imaging is recommended in certain women (Table 1).[5,5a]

The use of biochemical markers of bone turnover in diagnosis and fracture risk prediction is an area of active research. At present, however, standardized reference ranges, collection procedures and guidelines for their use are lacking.

Diagnosis

The World Health Organization has established diagnostic categories for women using BMD or bone mineral content.[7] A normal BMD/bone mineral content is within 1 standard deviation of index (T score ≥−1), whereas low bone mass (osteopenia) is defined as a T score of −2.5 to <−1. Osteoporosis is diagnosed by a T score ≤−2.5, whereas severe or established osteoporosis requires the addition of one or more fragility fractures for diagnosis.[7]

The occurrence of a fragility fracture constitutes clinical osteoporosis, regardless of T score,[5] and osteopenia at high risk of fracture can be identified using the fracture risk assessment tool (FRAX), which estimates fracture risk using age, sex, body weight/body mass index, personal fracture history, parental hip fracture history, current smoking status, excessive alcohol use, physician-confirmed rheumatoid arthritis, glucocorticoid use (≥5 mg prednisone daily for ≥3 months), secondary causes of osteoporosis, and femoral neck BMD as variables.[8] In postmenopausal women, FRAX has been validated only in untreated patients with T scores from −1.0 to −2.5 and no prior hip/vertebral fractures. "Fracture" in this algorithm is a broken bone (excluding skull, face, hand, or foot) after age 50 years.[9]

Patients Warranting Intervention

Treatment should be considered in postmenopausal women with a hip or (clinical or radiographic) vertebral fracture (ie, clinical osteoporosis), a T score of ≤−2.5 at the femoral neck, total hip, or spine (with or without fractures, ie, osteoporosis or severe/established osteoporosis), or a T score of −1.0 to −2.5 at the femoral neck or lumbar spine plus a 10-year probability of either hip fracture ≥3% or major osteoporosis-related fracture ≥20% by FRAX calculation (ie, osteopenia at high risk for fracture).[5a] Preventive measures, however, should be addressed in all peri- or postmenopausal women.

Prevention

Options to prevent postmenopausal osteoporosis include avoiding some lifestyle factors and encouraging others and hormone therapy.

Lifestyle Factors to Avoid

Smoking and excessive consumption of alcohol and/or caffeine should be avoided. Smoking accelerates radial bone loss after menopause,[10] hastens femoral neck bone loss in elderly adults,[11] and is associated with a significantly increased fracture risk.[12,13] Although some studies demonstrated higher

bone densities in postmenopausal women who consumed moderate amounts of alcohol (≥7 oz weekly or more than two drinks daily),[14,15] others identified an increased risk of falls in adults aged 25 to 60 who consumed two alcoholic drinks within 6 hours[16] and an increased fracture risk with ingestion of >2 U (approximately 16 g) of alcohol daily.[17] One study found accelerated spinal bone loss in elderly women consuming >300 mg of caffeine daily,[18] and high caffeine intake is associated with an increased fracture risk.[19,20]

Although falls are not considered a risk factor for osteoporosis per se, most osteoporosis-related fractures result from falls.[3] Some factors that contribute to fall risk (age, female sex, history of previous falls) cannot be modified, whereas others (poor muscle strength, impaired balance or vision, vitamin D insufficiency, use of psychotropic medications or sedatives, and environmental/home fall hazards) should be addressed whenever possible.[3,5,5a]

Lifestyle Factors to Encourage

Adequate calcium and vitamin D intake are necessary to prevent and treat postmenopausal osteoporosis,[3,5,5a] although their effect on bone density and fracture risk is complex. Calcium supplementation (approximately 1000 mg daily) appeared to significantly prevent bone loss over 4 years in postmenopausal women in one meta-analysis,[21] and the Women's Health Initiative (WHI) found that daily ingestion of 1000 mg elemental calcium and 400 IU vitamin D_3 produced a small but significant improvement in hip bone density, reducing hip fracture risk by 29% among women with ≥80% regimen adherence, by 21% among those 60 years old or older at enrollment; and by 30% among women not taking other calcium supplements.[22,23] Other studies and reviews support the efficacy of similar calcium supplementation in compliant patients[24] and in combination with vitamin D,[25] and a Cochrane review suggested that vitamin D alone was unlikely to prevent fractures.[25] A meta-analysis of vitamin D supplementation in ambulatory or institutionalized older adults suggested that 400 IU daily did not reduce fracture risk; however, 700 to 800 IU daily reduced the risk of hip and nonvertebral fractures by 26% and 23%, respectively.[26] The NOF recommends 1200 mg/day and 800 to 1000 IU/day for women 51 years old and older and 50 years old and older, respectively.[5a] Although diet is the preferred calcium source, most women need to add 600 to 900 mg daily as supplements.[5] Adult daily intake probably should not exceed 2500 mg calcium or 2000 IU vitamin D,[27] although lower limits for calcium and higher limits for vitamin D are suggested by some experts.[5a,28]

Possible adverse effects of supplementation have been identified. A meta-analysis raised concerns that calcium supplementation (with or without supplemental vitamin D) may modestly increase cardiovascular risk[29]; several limitations of this study, combined with conflicting reports of reduced vascular events with higher (dietary) calcium intake,[30] leave this issue in dispute and do not alter NOF recommendations to date. Although the WHI suggested that calcium and vitamin D supplementation increased the risk of nephrolithiasis among women consuming approximately 2150 mg of calcium daily,[22,23] others reported a decreased overall risk with higher dietary calcium intake,[31–33] noting that age-defined subgroups demonstrate different risks from calcium supplementation.[32,33] In light of these conflicting data, dietary calcium may be a safer option for patients predisposed to kidney stones, but supplements can be considered if diet modification proves inadequate.

Screening for and correcting inadequate vitamin D serum concentrations (with 25-hydroxyvitamin D level <20 ng/mL defining deficiency and 21–29 ng/mL representing insufficiency)[34] also are necessary, because up to 41% of selected patients may be affected.[35] Vitamin D inadequacy (<30 ng/mL) has been documented in 52% of postmenopausal women receiving osteoporosis therapy in a North American trial[36] and in 64% of osteoporotic women in an international study.[37] Community-dwelling ambulatory older women with a history of falls and vitamin D insufficiency experienced an approximate 19% reduction in relative risk of falls when treated with ergocalciferol (25-hydroxyvitamin D_2),[38] a benefit similar to that demonstrated among supplemented ambulatory or institutionalized older adults[39] and believed to be related to preserved muscle strength and functional ability.[40] Vitamin D deficiency can be treated with 50,000 IU of oral ergocalciferol once weekly for 8 weeks[35,41] in patients with normal renal function, followed by another 8-week course if levels remain low.[41]

Exercise in postmenopausal women decreases bone loss,[42] strength/resistance and weight training preserve or improve BMD at the spine and various hip sites,[43–45] and walking similarly benefits the femoral neck.[46] A multicomponent (strength, aerobic capacity, balance, joint mobility), dual-modality (ground and water) exercise regimen significantly improves femoral neck T score and physical functional capacity in postmenopausal women with low BMD.[47] Quadriceps strengthening and proprioceptive training prevent falls and improve muscle power, static and dynamic balance, and the speed of motor responses in affected women.[48] Structured exercise, therefore, should be recommended in postmenopausal women, excluding high-impact aerobics and fall-prone activities in those with established osteoporosis.[5]

Hormone Therapy

Estrogen therapy (ET) and combined hormone therapy (HT; estrogen-progestin for women with intact uteri) are approved for osteoporosis prevention and relief of menopausal symptoms.[3] Combined HT reduced the risk of clinical vertebral and hip fractures by 34% and other osteoporotic fractures by 23%, but it appeared to increase risks of other serious conditions (myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein phlebitis) in 5 years of treatment in the WHI[49]; however, no significant increase in cardiovascular disease was demonstrated among

Table 2. Key trials showing efficacy of medications in reducing fracture risk

Acronym/ length of study	Drug vs placebo	No. patients	Baseline characteristics	RR or relative HR	RR reduction
FIT 1[52]/3 y	Alendronate 5 mg/d × 24 mo, then 10 mg/d or placebo	2027	Women, aged 55–81, low BMD, morphometric vertebral fractures on radiographs	Vertebral 0.53, hip 0.49	Vertebral 47%, hip 51%
VERT-NA[53]/3 y	Risedronate 2.5 mg/d (discontinued >1 y), 5 mg/d, or placebo	2458	Ambulatory women, aged 85 y or younger, 5 y since menopause, ≥2 vertebral fractures, or 1 vertebral fracture and low lumbar spine BMD	Vertebral 0.59, hip NA	Vertebral 41%, hip NA
VERT-MN[54]/3 y	Risedronate 2.5 mg/d, 5 mg/d, or placebo	1226	Postmenopausal women with ≥2 vertebral fractures	Vertebral 0.51, hip NA	Vertebral 49%, hip NA
HIP[55]/3 y	Risedronate 2.5 mg/d, 5 mg/d, or placebo	9331	Women, aged 70–79 y, osteoporosis (5445 patients) or women, age 80 or older with 1 nonskeletal risk factor for hip fracture or low BMD at the femoral neck (3886 patients)	Vertebral NA, hip 0.70 overall (0.60 in women 70–79 y old with osteoporosis)	Vertebral NA, hip 30% (40% in women 70–79 y old with osteoporosis)
BONE[56] /3 y	Ibandronate 2.5 mg/d, 20 mg every other day for 12 doses every 3 mo, or placebo	2946	Women, aged 55–80 y, ≥5 y postmenopausal, 1–4 prevalent vertebral fractures (T4–L4), and a BMD T score of −2.0 to −5.0 in at least 1 vertebra (L1–L4)	Vertebral 0.38 (daily dosing), 0.50 (intermittent dosing); hip NA	Vertebral 62% (daily dosing), 50% (intermittent dosing); hip NA
HORIZON[57]/3 y	Zoledronic acid 5 mg IV or placebo at 0, 12, and 24 mo	3889	Postmenopausal women, aged 65–89 y, BMD T score ≤−2.5 at the femoral neck ± vertebral fracture or a T score ≤−1.5 with radiologic evidence of at least 2 mild vertebral fractures or 1 moderate vertebral fracture	Vertebral 0.30, hip 0.59	Vertebral 70%, hip 41%
MORE[58]/3 y	Raloxifene 60 mg/d, 120 mg/d, or placebo	7705	Women, aged 31–80 y, postmenopausal for 2 y, met WHO criteria for osteoporosis	Vertebral 0.7 (60 mg/d), 0.5 (120 mg/d); hip NA	Vertebral 30% (60 mg/d), 50% (120 mg/d); hip NA
FPT[59]/median treatment duration 21 mo	Teriparatide 20 μg, 40 μg, or placebo SC daily	1637	Women, ≥5 y postmenopausal, at least 1 moderate or 2 mild atraumatic vertebral fractures on radiographs of thoracic and lumbar spine, ambulatory status; if <2 moderate fractures a T score for BMD of hip or lumbar spine of at least −1 required	Vertebral 0.35 (20 μg), 0.31 (40 μg); hip NA	Vertebral 65% (20 μg), 69% (40 μg); hip NA
FREEDOM[60]/3 y	Denosumab 60 mg SC every 6 mo or placebo	7868	Women, aged 60–90 y, BMD T score <−2.5, not <−4.0 at lumbar spine or total hip	Vertebral 0.32, hip 0.60	Vertebral 68%, hip 40%
PROOF[61]/5 y	Calcitonin (salmon calcitonin nasal spray) 100, 200, or 400 IU or placebo daily	1255	Postmenopausal women with established osteoporosis	Vertebral 0.67 (200 IU group), hip NA	Vertebral 33% (200 IU group), hip NA

BMD, bone mineral density; BONE, oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe; FIT 1, Fracture Intervention Trial; FPT, Fracture Prevention Trial; FREEDOM, Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; HIP, Hip Intervention Program; HORIZON, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly; HR, hazard ratio; IV, intravenous; MORE, Multiple Outcomes of Raloxifene Evaluation; NA, not available; PROOF, Prevent Recurrence of Osteoporotic Fractures; SC, subcutaneous; VERT-MN, Vertebral Efficacy With Risedronate Therapy-Multinational; VERT-NA, Vertebral Efficacy With Risedronate Therapy-North America; WHO, World Health Organization.

women who started HT within 10 years of menopause,[50] and no increase in breast cancer incidence was seen among women receiving ET alone.[51]

The NOF recommends ET/HT in low doses with short duration for moderately severe menopausal symptoms.[5a] The NAMS recommends that the primary indication for ET/HT should be treatment of moderate to severe menopausal symptoms; however, when symptoms are controlled, continued therapy can be considered for bone effects (after considering the risks and benefits in an individual patient).[5] The Food and Drug Administration advises that other approved non-ETs should be considered first.[3]

Summary of Preventive Recommendations

Based on available evidence, the consensus opinion is to recommend avoidance of smoking, excess alcohol, or excess caffeine; fall prevention measures; calcium 1000 to 1200 mg

daily (diet or supplements); vitamin D 800 to 1000 units daily if replete; and structured exercise. HT should not be initiated for osteoporosis prevention alone.

Treatment

Treatment of postmenopausal osteoporosis should include continuing preventive measures, identifying and addressing additional contributing factors, and introducing drug therapy. Potentially remediable contributors include hypercalciuria, diabetes, hyperparathyroidism, thyrotoxicosis, celiac disease, multiple myeloma, hypovitaminosis D, and medications such as anticoagulants, anticonvulsants, proton pump inhibitors, and corticosteroids.[5a] In addition to the history and physical examination, clinicians may check complete blood counts, metabolic panels (including calcium, magnesium, and phosphorus) thyroid-stimulating hormone, 25-hydroxy vitamin D, parathyroid hormone, 24-hour urine for calcium and creatinine, and, if appropriate, serum and urine protein electrophoresis and a celiac panel.[3]

Drugs that have been approved in the United States for the prevention and/or treatment of postmenopausal osteoporosis (in addition to preventive ET/HT) include the bisphosphonates, raloxifene, parathyroid hormone, denosumab, and calcitonin.[3] Several key studies demonstrate the efficacy of these medications in reducing vertebral and/or hip fracture risk (Table 2).[52–61] Alendronate, risedronate, zoledronic acid, and denosumab reduce spine and hip fracture risk, and ibandronate, raloxifene, parathyroid hormone, and calcitonin reduce vertebral fractures.

Bisphosphonates constitute first-line therapy for most patients because they inhibit bone resorption by reducing recruitment and activity of osteoclasts and increasing osteoclast apoptosis, preventing further bone loss while moderately increasing BMD.[62] Of those available in the United States, alendronate, risedronate, and zoledronic acid are approved for the prevention and treatment of postmenopausal osteoporosis, whereas ibandronate is approved only for treatment.[3] Alendronate and risedronate are oral medications, zoledronic acid is an intravenous preparation, and ibandronate can be administered by either route.[3] Patients must take oral bisphosphonates with 8 oz of water upon awakening, then wait 30 minutes (60 minutes for ibandronate) before reclining, eating, drinking, or taking other medications.[3] Contraindications include hypocalcemia (all bisphosphonates), esophageal diseases that delay emptying (stricture, achalasia) or an inability to remain upright for 30 to 60 minutes after administration (oral bisphosphonates),[6] and acute renal impairment (zoledronic acid).[63] Bisphosphonates are contraindicated in patients with creatinine clearance <35 mL/min (zoledronic acid) or not recommended at creatinine clearance <30 (risedronate, ibandronate) to 35 (alendronate) mL/min.[63] Calcium and vitamin D should be adequately replaced before starting any bisphosphonate.[63] Adverse effects include upper gastrointestinal adverse effects, hypocalcemia, hypophosphatemia, musculoskeletal pain, worsening of renal impairment (with zoledronic acid),[63] acute-phase reactions (fever, influenza-like illness),[63] increased risk of osteonecrosis of the jaw (ONJ), the presence of exposed maxillofacial bone that does not heal within 8 weeks of diagnosis),[64] and atypical subtrochanteric and diaphyseal femoral fractures.[63] Data regarding a possible risk of atrial fibrillation with bisphosphonates have been conflicting.[63]

Three adverse effects warrant further discussion. ONJ occurs with a frequency of between 1 in 10,000 and <1 in 100,000 patient-treatment years in those taking bisphosphonates for osteoporosis.[64] Risk factors include underlying periodontal disease, diabetes mellitus, hypothyroidism, corticosteroid or cancer chemotherapeutic drug use, excessive alcohol intake, smoking, head and neck radiation, and dental procedures involving bone manipulation.[65] Good oral hygiene, regular dental examinations and cleanings, and heightened care when undergoing local surgical procedures (chlorhexidine rinses, possibly prophylactic antibiotics) help prevent ONJ. Management consists of oral antibiotic rinses such as chlorhexidine with or without antibiotics for secondary infection, and debridement or resection when necessary.[65] Practitioners may review appropriate references for more detail.

Although the overall risk for atypical subtrochanteric fractures with bisphosphonates is small (32 cases per million person-years in one study), it does appear greater with prolonged treatment, particularly with continuous use for ≥5 years.[66] Patients who develop one such fracture are at particularly high risk for contralateral fractures.[66]

Studies have found conflicting estimates of the esophageal cancer risk associated with oral bisphosphonates, even between cohorts from the same database—one concluding that the risk increased with ≥10 prescriptions for oral bisphosphonates or use for >3 years,[67] and another showing no increased risk.[68] Clarification awaits further study.

Raloxifene, an estrogen agonist/antagonist, is approved for use in postmenopausal women to prevent and treat osteoporosis and to reduce risk of invasive breast cancer during osteoporosis treatment or for patients at high cancer risk.[3,63] It is contraindicated in patients with a history of venous thromboembolic disease[63] and should be used with caution in women with hepatic or moderate to severe renal impairment. Adverse reactions may include worsening of preexisting hypertriglyceridemia, venous thromboembolism, vaginal bleeding, and hot flashes. Monitoring plasma lipid levels and for evidence of uterine bleeding and breast abnormalities is recommended during treatment.[63]

Teriparatide (parathyroid hormone) is an anabolic agent approved to treat osteoporosis in postmenopausal women at high fracture risk.[3] An increased incidence of osteosarcoma in animal studies has limited the recommended treatment duration to ≤2 years.[63] It should be avoided in women with Paget disease of bone, unexplained alkaline phosphatase elevations, prior skeletal radiotherapy, primary or metastatic bone malignancy, and hypercalcemic disorders (eg, primary

Table 3. Drugs approved by FDA for treatment of postmenopausal osteoporosis

Drug	Indications for postmenopausal osteoporosis		Contraindications/warnings	Risk for specific adverse effects				
	Prevention	Treatment		Hypocalcemia	Osteonecrosis of jaw	Subtrochanteric or atypical fractures	Osteosarcoma	Venous thromboembolism
Alendronate	X	X	Hypocalcemia	X	X	X		
			Esophageal diseases that delay emptying					
			Inability to remain upright for 30 min					
			Not recommended at creatinine clearance <35 mL/min					
			Calcium and vitamin D should be adequately replaced					
Risedronate	X	X	Hypocalcemia	X	X	X		
			Esophageal diseases that delay emptying					
			Inability to remain upright for 30 min					
			Not recommended at creatinine clearance <30 mL/min					
			Calcium and vitamin D should be adequately replaced					
Ibandronate		X	Hypocalcemia	X	X	X		
			Esophageal diseases that delay emptying (oral form)					
			Inability to remain upright for 60 min (oral form)					
			Not recommended at creatinine clearance <30 mL/min					
			Calcium and vitamin D should be adequately replaced					
Zoledronic acid	X	X	Hypocalcemia	X	X	X		
			Acute renal impairment					
			Contraindicated at creatinine clearance <35 mL/min					
			Calcium and vitamin D should be adequately replaced					
Raloxifene	X	X	Contraindicated in patients with a history of venous thromboembolic disease					X
			Used with caution in women with hepatic or moderate to severe renal impairment					
Teriparatide		X (in women at high risk of fracture)	Do not use >2 y				X (animal studies)	
			Avoid in Paget disease of bone, unexplained alkaline phosphatase elevations, prior skeletal radiotherapy, primary or metastatic bone malignancy, hypercalcemic disorders					
			Caution in patients with urolithiasis or hypercalciuria					
Denosumab		X (in women at high fracture risk)	Contraindicated in hypocalcemia	X	X	X		
			Calcium deficiency must be corrected					
			Patients with renal impairment are at significant risk for hypocalcemia					
			Adequate calcium/vitamin D supplementation required					
Salmon calcitonin		X (in women >5 y after menopause)	Consider skin testing for serious allergic reaction	X				
			Risk of hypocalcemic tetany with injected form					
			Concern for cancer risk					

FDA, Food and Drug Administration.

hyperparathyroidism),[3,63] and should be used with caution in patients with urolithiasis or hypercalciuria.[63]

Denosumab, a receptor activator of nuclear factor-κB ligand inhibitor[69] also is approved to treat women with postmenopausal osteoporosis at high fracture risk.[63] Contraindicated in the presence of hypocalcemia, calcium deficiency must be corrected before treatment initiation. Patients with renal impairment are at significant risk for hypocalcemia with treatment and all patients require adequate concurrent calcium/vitamin D supplementation during therapy.[63] Serious infections, skin rashes, musculoskeletal pain, and hypercholesterolemia have been reported during use.[63] This drug may suppress bone turnover, contributing to ONJ, atypical fractures, and delayed fracture healing.[63]

Salmon calcitonin, a hormonal inhibitor of bone resorption, is approved to treat osteoporosis in women >5 years after menopause and is available as an injection or nasal spray.[63] Serious allergic reactions have been reported and skin testing before treatment can be considered.[63] Injected calcitonin may lead to hypocalcemic tetany and parenteral calcium should be available during the first several administrations.[63] Urinary sediment should be monitored for casts, and mucosal examinations performed regularly when the drug is inhaled.[63] A Food and Drug Administration advisory group concluded that its benefits in postmenopausal osteoporosis do not outweigh an uncertain cancer risk association.[70]

Table 3 summarizes the indications, contraindications/warnings, and some potential adverse effects of the approved therapies. There is no consensus regarding the duration of therapy or frequency of monitoring for response to therapy. The NAMS notes that repeat DEXA may not provide useful information until at least 1 to 2 years of treatment. A stable BMD identifies therapeutic success: fracture risk reductions from antiresorptive therapy are similar whether BMD is unchanged or increased[5]; however, marked declines in BMD predict greater fracture risk and should trigger reevaluation for secondary contributors or medication nonadherence.[5]

Summary of Treatment Recommendations

Although individual patient characteristics should influence treatment decisions, based on efficacy, cost, and long-term safety data, consensus opinion recommends bisphosphonates, particularly alendronate or risedronate, as first-line postmenopausal osteoporosis therapy in most patients. Raloxifene should be considered in patients at high risk of invasive breast cancer, and teriparatide or denosumab can be considered in osteoporotic patients at high risk of fracture. Optimal length of therapy is unknown because the risk benefit of long-term pharmacologic osteoporosis therapy remains undefined.

Conclusions

Postmenopausal osteoporosis causes significant morbidity and mortality. Nonpharmacologic preventive measures should be initiated at or near menopause, with drug treatment added as indicated for patients with osteopenia at high fracture risk or frank osteoporosis. Bisphosphonates are recommended as first-line therapy in most patients, and raloxifene should be considered in patients at high risk for invasive breast cancer and teriparatide or denosumab in patients at high fracture risk. Optimal frequency of monitoring and duration of therapy require further study.

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