New Approaches to the Management of Osteoporosis

Introduction

Osteoporosis affects approximately 10 million men and women in the United States, with osteopenia, or low bone mass, affecting an additional 34 million. Fractures, particularly hip and vertebral, are associated with significant pain, disability, loss of independence, financial expense, and increased mortality. Ongoing advances in diagnosis, risk assessment, and pharmacologic and nonpharmacologic interventions offer the means to reduce fractures and associated morbidity and mortality in at-risk populations. Pharmacists are positioned to be pivotal health care professionals in the prevention and management of osteoporosis. Within the context of two case studies, this Highlights Newsletter will equip pharmacists to further expand their role to include assessing fracture risk, recommending bone mineral density (BMD) testing, encouraging a bone-healthy lifestyle, counseling patients on over-the-counter and prescription medications, individualizing prevention and treatment plans, managing adverse events, and improving medication adherence.

Case 1. Primary Osteoporosis

Ten years ago, at age 65 years, Kathy had a routine physical with her primary care provider. A newly retired and active white woman, Kathy's medical history included hypertension, treated with hydrochlorothiazide 25 mg daily, and occasional heartburn, managed with an over-the-counter antacid as needed. Her height and weight were stable at 5 feet 4 inches and 149 lb, respectively. She reported smoking approximately 1 pack of cigarettes per day and drinking 1 glass of wine per month. She took no multivitamin or other supplements, including calcium, and avoided dairy products. Neither of her parents had a fracture as an adult. A dual-energy x-ray absorptiometry (DXA) scan to measure BMD was performed and showed the following T-scores: –1.8, total hip; –1.9, femoral neck; and –1.6, lumbar spine. Her health care provider recommended no pharmacologic therapy at this time, but advised bone-healthy lifestyle modifications.

Now, at 75 years of age, Kathy’s height has decreased to 5 feet 3 inches, and her weight has increased to 154 lb. For 8 years, her heartburn has been treated with omeprazole 20 mg daily. Her hypertension remains well controlled with hydrochlorothiazide. Her habits have not changed and she continues to smoke. A repeat DXA scan demonstrated bone loss with T-scores of –2.0, total hip; –2.3, femoral neck; and –1.9, lumbar spine.

Epidemiology and Pathogenesis of Osteoporosis

Osteoporosis is a skeletal disease characterized by decreased bone strength due to low bone mass and deterioration of bone microarchitecture, resulting in increased bone fragility and risk of fracture, particularly of the spine, hip, and wrist. Although the disease affects women and men, it is more common in women. Of the 10 million individuals with osteoporosis, 80% are women. The prevalence of osteoporosis increases with age: from 4% in women aged 50 to 59 years up to 52% in women 80 years and older. Among postmenopausal women, blacks have the lowest rate of osteoporosis.

Questions to Ask About This Case

- What is the epidemiology and pathogenesis of osteoporosis?
- How is a patient evaluated for osteoporosis and risk of fracture?
- What nonpharmacologic interventions should be recommended?
- What are the pharmacologic prevention and treatment options?
- What treatment-related adverse events should be considered?
- What instructions should be given to the patient regarding therapy?
(4%) and Native Americans have the highest (12%), followed by Asians and Hispanics (both 10%), and whites (7%).

More than 2 million osteoporosis-related fractures occur each year (vertebral, 547,000; wrist, 397,000; hip, 297,000; pelvic, 135,000; and other, 675,000). Morbidity associated with these fractures is costly in terms of individual and societal burden. Approximately one third of fractures overall and nearly all hip fractures result in hospitalization. A hip fracture increases the risk of mortality within 1 year by up to 25%, necessitates long-term care in one quarter of cases, and results in long-term decreases of mobility in one half of cases. Vertebral fractures cause pain, loss of height, restricted physical movement, including breathing, and increased risk of future vertebral fracture. Direct health care cost of osteoporosis-related fractures was $19 billion in 2005, with a projected increase to $25.3 billion by 2025.

Bone is continually being remodeled through the dual processes of osteoclast-mediated bone resorption and osteoblast-mediated bone formation (Figure 1). Resorption is triggered when osteocytes and cells lining the bone surface release cytokines and growth factors that signal osteoclasts to release receptor activator of nuclear factor κB–ligand (RANK-ligand, or RANKL). RANKL then binds to the receptor RANK on the surface of osteoclast precursors, causing differentiation of osteoclasts, and on the

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**LEARNING OBJECTIVES**

At the completion of this activity, the pharmacist will be able to:

- Describe the epidemiology, etiology, and pathophysiology of osteoporosis and apply this knowledge to identify individuals who are at risk of fracture and educate them about the disease.
- Discuss the morbidity, mortality, and health care costs associated with osteoporosis and assess the potential burden of disease in the pharmacist’s current patient population.
- Formulate effective patient-specific treatment regimens based on the mechanism of action, efficacy, and safety data of current and emerging osteoporosis pharmacologic and nonpharmacologic agents.
- Recall current guidelines and advances in osteoporosis management and integrate these approaches into care plans for patients with osteoporosis or at risk of fracture.
- Assess patient medication and bone-healthy lifestyle adherence and develop a plan with the patient to improve adherence.
- Outline a plan to expand current pharmacy services by including more osteoporosis prevention and treatment services.

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New Approaches to the Management of Osteoporosis

Highlights Newsletter:

Men because they are affected by rapid primary osteoporosis compared with to three times more likely to develop tion.

Continued resorption by osteoclasts. Osteoclasts release integrin, which forms an osteoclast-bone seal, as well as cathepsin K and other chemicals that create an acidic microenvironment and demineralize bone. This process is downregulated when osteoclasts produce osteoprotegerin, which binds to RANKL preventing it from binding to RANK, reversing the remodeling course from destruction to formation. Proteins and minerals, including calcium, are then deposited to rebuild bone.

In healthy young adults, normal bone balance is maintained by equal rates of resorption and formation. Bone loss occurs when resorption surpasses formation through excessive resorption or inadequate bone formation. If bone loss is great enough over time, osteoporosis results. For individuals who have suboptimal peak bone mass and bone strength attributable to genetics, diet, or lifestyle, bone loss may more quickly pass the osteoporosis threshold.

Primary osteoporosis is due to the effects of aging and estrogen deficiency on bone. With aging, osteoblasts lose their ability to build bone despite continued resorption by osteoclasts. In the setting of estrogen deficiency, osteoclasts become hyperactive and increase bone resorption beyond the osteoblasts’ capacity to compensate with formation. Postmenopausal women are two to three times more likely to develop primary osteoporosis compared with men because they are affected by rapid postmenopausal bone loss due to estrogen deficiency, as well as gradual aging-related bone loss. Secondary osteoporosis may be caused by numerous medications and disorders with adverse effects on the skeleton (TABLE 1). In men, osteoporosis is commonly due to a secondary cause or hypogonadism (low testosterone).

Patient Risk Assessment

Risk assessment is based on a thorough evaluation of risk factors for bone loss and fracture, including the risk of falling, and BMD testing. FRAX, the new fracture risk assessment tool developed by the World Health Organization, utilizes identified risk factors, with or without BMD data, to calculate a 10-year probability of fracture. Altogether, this information helps health care providers recommend steps to reduce fracture risk through prevention or treatment of osteoporosis.

Evaluating for Risk Factors

Age and sex steroid deficiency, due to menopause or hypogonadism, are the primary risk factors for bone loss and fracture. Additional risk factors include those related to lifestyle and genetics, as well as medications and medical conditions that are secondary causes of osteoporosis due to their adverse effect on the skeleton (TABLE 1). Lifestyle-related factors that compromise skeletal health include lack of exercise, smoking, inadequate calcium and vitamin D intakes, 3 or more alcoholic drinks daily, low body mass index, and a likelihood of falling. Prior low-trauma fracture as an adult significantly increases the risk of new fracture. Hip fracture in a parent also indicates a higher risk of fracture.

Table 1. Selected Factors That Cause or Contribute to Osteoporosis and Related Fracture

<table>
<thead>
<tr>
<th>Lifestyle Factors</th>
<th></th>
<th></th>
<th>Medications</th>
<th></th>
<th></th>
<th>Conditions or Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate intake of calcium or vitamin D</td>
<td>Alcohol (≥3 drinks per day)</td>
<td>Smoking</td>
<td>Inactivity or immobility</td>
<td>Underweight</td>
<td>Current or history of falling</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Gonadotropin-releasing hormone agonists</td>
<td>Cytotoxic drugs</td>
<td>Aromatase inhibitors</td>
<td>Excessive thyroid supplementation</td>
<td>Long-term heparin</td>
<td>Depo-medroxyprogesterone acetate</td>
</tr>
<tr>
<td>Glucocorticoids (≥5 mg/d of prednisone or equivalent for ≥3 months)</td>
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<td></td>
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<td></td>
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</tbody>
</table>

Stop & Think

What were Kathy’s risk factors at 65 years old?
At 75 years old?
Assessing Risk of Falling. Seniors should be asked annually if they have fallen in the past 12 months and if they have difficulty with walking or balance. Those with a positive history should be further evaluated with a multifactorial risk assessment including a review of medical conditions and current medications; a physical examination for neurologic function, muscle strength, cardiovascular status, visual acuity, and condition of feet and footwear; a functional assessment of current activity, use of adaptive equipment, and fear related to falling; and a home safety check.

BMD Testing. Central DXA testing of the hip (femoral neck or total hip) and lumbar spine is the gold standard for measuring BMD and diagnosing osteoporosis. The one-third radius site also may be used if the femoral neck or lumbar spine sites are not available. While other technologies, such as computed tomography–based absorptiometry, ultrasound, or peripheral DXA of the finger or heel also may predict fracture risk, only measurements from central DXA may be used for diagnosis.

DXA measures areal BMD, defined as grams of bone mineral divided by the total area of scanned bone (g/cm²), and reports this measurement as a T-score or a Z-score. T-scores are used for postmenopausal women and for men aged 50 years and older, and reflect a comparison between the patient’s BMD and the average for young normal adults of the same sex. Z-scores, which compare the patient’s BMD and the expected BMD for a reference standard of adults near the same age and of the same sex, are used to evaluate bone health in premenopausal women and men aged 50 years and younger; they also can reflect potential secondary causes. A T-score of –2.5 or below at any measured site indicates a diagnosis of osteoporosis, while a T-score between –1.0 and –2.5 indicates low bone mass, or osteopenia. A T-score of –1.0 and above is normal. Severe, or established, osteoporosis is defined as a T-score of –2.5 or below and the occurrence of at least one fragility fracture.

BMD testing is recommended for the following individuals who are at risk for bone loss and may benefit from treatment:

- Postmenopausal women younger than age 65 years and men aged 50 to 69 years with risk factors for fracture.
- Perimenopausal women with one or more clinical risk factors for fracture, such as low body weight or high-risk medication.
- Postmenopausal women discontinuing estrogen.
- Adults who have a low-trauma, or fragility, fracture.
- Adults with a condition or disorder or taking a medication associated with low bone mass or bone loss.
- Anyone being considered for pharmacologic therapy for osteoporosis.
- Anyone being treated for osteoporosis (to monitor treatment response).
- Anyone who may be a candidate for therapy given evidence of bone loss.

Heel Ultrasound. Heel ultrasound can be used only for screening, not for diagnosis. Additionally, it should be used only for postmenopausal women, perimenopausal women with significant risk, and men older than 65 years of age. The T-score indicating the need to refer the patient for a diagnostic BMD by DXA varies by manufacturer.

FRAX. FRAX is a free online tool available at www.shef.ac.uk/FRAX/. It uses a specific set of identified risk factors to calculate an individual’s 10-year probability of a major osteoporotic fracture (i.e., clinical vertebral, hip, forearm, or shoulder fracture) and 10-year probability of hip fracture. Separately calibrated calculators are available at the FRAX website for four U.S. groups—whites, blacks, Hispanics, and Asians—as well as multiple countries. It is intended for use in untreated postmenopausal women and men aged 50 years and older.

FRAX requires input of numerical data for weight, height, and age (Figure 2). It also asks for femoral neck BMD (g/cm²) or T-score, but can be used in the absence of both. Dichotomous data (yes or no) are required regarding prior low-trauma fracture as an adult, parental history of hip fracture, current smoking, glucocorticoid use (current or past use of oral glucocorticoids for more than 3 months at a dose of prednisone of 5 mg daily or more, or equivalent doses of other glucocorticoids), alcohol intake of 3 or more units daily, rheumatoid arthritis, and secondary osteoporosis (enter “yes” if the patient has a disorder strongly associated with osteoporosis, including type 1 diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause [younger than 45 years], chronic malnutrition or malabsorption, and chronic liver disease).

Stop & Think
For Kathy at ages 65 and 75 years, determine her 10-year probability of a major osteoporotic fracture and 10-year probability of hip fracture using the online FRAX tool. Remember to choose the appropriate calculator.
Nonpharmacologic Interventions

Universal recommendations for all individuals include an adequate intake of calcium and vitamin D, regular weight-bearing and muscle-strengthening exercise, avoidance of tobacco use, and alcohol consumption limited to no more than 2 drinks per day.10 Other modifiable risk factors, including those related to falling, also should be minimized as much as possible.

Calcium. The National Osteoporosis Foundation recommends women over the age of 50 years should consume 1,200 to 1,500 mg of elemental calcium per day, either through diet or supplementation.10 Good food sources of calcium include dairy products, some vegetables, and calcium-fortified foods and beverages. Calcium supplements are available as oral tablet, chewable, or liquid forms and may be combined with vitamin D or other nutrients for bone health. Calcium carbonate (40% elemental calcium) requires an acidic medium for proper disintegration and dissolution and thus must be taken with food.19 Use of high or daily doses of proton pump inhibitors may inhibit the ability to disintegrate or dissolve calcium carbonate effectively. In contrast, calcium citrate (21% elemental calcium) does not require an acidic medium and may be taken independent of food.

Vitamin D. Vitamin D is needed for calcium absorption, muscle performance, balance, and fall prevention.20 Deficiency is common due to limited sun exposure, malabsorption, and its availability only in fatty fish and few fortified foods and beverages.10 To achieve the optimal serum 25-hydroxyvitamin D (25[OH]D) concentration of 30 ng/mL (75 nmol/L) or higher, all adults over the age of 50 years should have a daily vitamin D intake of 800 to 1,000 units. Some individuals may require a higher amount of supplementation, and the dose should be matched to the individual’s baseline 25(OH)D serum concentration. Individuals with concentrations below 30 ng/mL may require weekly or biweekly doses of 50,000 units of vitamin D for 8 to 12 weeks.21

Fall Prevention. Action should be taken to minimize all identified risk factors for falling, including but not limited to making safety improvements to the home, eliminating medications related to falls, beginning an exercise program to increase strength and balance, regulating blood pressure and blood glucose levels, and vitamin D supplementation.10

Bisphosphonates. Bisphosphonates work by inhibiting osteoclast activity, which then allows unopposed bone building by osteoblasts and decreased bone turnover.33 Alendronate, risendronate, and ibandronate have demonstrated the ability to reduce the relative risk of vertebral fractures by 40% to 50%, and intravenous zoledronic acid reduced the relative risk by approximately 70%.34-39 Alendronate, risendronate, and zoledronic acid also have demonstrated the ability to reduce the relative risk of nonvertebral fractures, including hip fractures, by approximately 20% to 50%, although the reductions did not approach statistical significance in all cases.34-37,39,40

The most common adverse effects associated with oral bisphosphonates are upper gastrointestinal symptoms, including nausea, abdominal pain, heartburn, esophageal irritation, ulcers, perforation, and bleeding.22,24,26 These symptoms may be minimized by strict adherence to recommended instructions for taking the medication. Some patients receiving oral or intravenous bisphosphonates have reported severe or incapacitating muscle, bone, and joint pain within days, months, or years of starting bisphosphonate therapy.41 In some cases pain resolves with discontinuation, while in other cases pain dissipates slowly or incompletely. Specific to intravenous administration is the potential for an acute-phase reaction producing fever, chills, and body aches within 3 days after injection.27,28

Osteonecrosis of the jaw (ONJ) is a serious, but rare, potential adverse effect of bisphosphonates, although no causal relationship has been established.42 ONJ also occurs with an unknown incidence within the general population in individuals not receiving bisphosphonates. Risk factors include tooth extraction or other invasive dental procedure, immunosuppressive therapy, and comorbid conditions, particularly multiple myeloma.42,43 ONJ occurs more frequently in persons receiving intravenous bisphosphonates for multiple myeloma, hypercalcemia of malignancy, or bone metastases of solid tumors at doses higher than used for osteoporosis treatment.43 Preferably, patients would have a dental examination prior to starting bisphosphonate therapy and once on therapy should consult their health care provider regarding any anticipated invasive dental procedure.

Pharmacologic Treatment Options for Primary Osteoporosis

Pharmacologic treatment options are categorized by whether they are antiresorptive (minimize bone destruction) or anabolic (build bone) (TABLE 2).4,10,22,32 Antiresorptive agents approved for prevention or treatment of osteoporosis in postmenopausal women include the bisphosphonates alendronate, risedronate, ibandronate, and zoledronic acid; raloxifene, an estrogen agonist-antagonist; calcitonin salmon, a synthetic polypeptide; and estrogen/hormone therapy. Currently, the only anabolic agent approved for use in postmenopausal osteoporosis is teriparatide, a recombinant parathyroid hormone. Some of these agents are also approved for the treatment of osteoporosis in men and glucocorticoid-induced osteoporosis.

The National Osteoporosis Foundation recommends pharmacologic treatment be considered for postmenopausal women and men older than age 50 years who have osteoporosis, as determined by a T-score less than or equal to –2.5 or a T-score between –1.0 and –2.5 at the femoral neck or spine, after secondary causes have been excluded, or who have already had a hip or vertebral fracture.10 In individuals with low bone mass (osteopenia; T-score between –1.0 and –2.5 at the femoral neck or spine), therapy candidacy is based on FRAX risk scores. Individuals with a 3% or greater 10-year probability of hip fracture or a 20% or greater 10-year probability of major osteoporosis-related fracture should be considered for therapy.

Stop & Think

At age 75 years, should Kathy be considered for pharmacologic treatment? On what basis?

Stop & Think

What nonpharmacologic interventions should have been included in the bone-healthy lifestyle recommendations given to Kathy at 65 years of age?
Atypical fractures of the subtrochanteric and diaphyseal femoral shaft, occurring with minimal or no trauma, have been reported in patients receiving bisphosphonates, although causality has not been fully determined. In response to this concern, the U.S. Food and Drug Administration (FDA) has reviewed all relevant case reports and clinical trial data and issued a statement concluding “these data did not show an increase in this risk in women using these medications.” The FDA will continue to monitor reports through its MedWatch system, and patients are advised to remain on prescribed bisphosphonate therapy but report any new hip or thigh pain to their health care providers.

Contraindications to oral bisphosphonates include abnormalities of the esophagus, such as stricture or achalasia that delay esophageal emptying, and the inability to remain upright for the required duration after taking the dose. Hypocalcemia must be corrected prior to starting therapy.

**Table 2. Agents Approved for the Prevention or Treatment of Osteoporosis in Postmenopausal Women**

<table>
<thead>
<tr>
<th>Category and Drug Class</th>
<th>Agent</th>
<th>Formulation</th>
<th>Approval</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiresorptive Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Alendronate</td>
<td>Oral tablet and oral solution</td>
<td>X</td>
<td>X&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral tablet, plus vitamin D (combination product)</td>
<td>—</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Risedronate</td>
<td>Oral tablet</td>
<td>X</td>
<td>X&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral tablet with calcium tablet (co-packaged product)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Ibandronate</td>
<td>Oral tablet</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Zoledronic acid</td>
<td>Intravenous</td>
<td>X</td>
<td>X&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Estrogen agonist-antagonist</td>
<td>Raloxifene</td>
<td>Oral tablet</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Synthetic polypeptide</td>
<td>Calcitonin salmon</td>
<td>Nasal spray</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcutaneous</td>
<td>—</td>
<td>100 units daily</td>
</tr>
<tr>
<td></td>
<td>Hormone therapy</td>
<td>Estrogen +/-progestogen</td>
<td>Multiple</td>
<td>X</td>
</tr>
<tr>
<td><strong>Anabolic Agent</strong></td>
<td>Recombinant human parathyroid hormone</td>
<td>Teriparatide</td>
<td>Subcutaneous</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup>Approved for the treatment of osteoporosis in men.

<sup>b</sup>Approved for the treatment of glucocorticoid-induced osteoporosis.

*Source: References 4, 10, and 22–32.*

Raloxifene reduces the relative risk of vertebral fracture by 30% to 50% over 3 years, but has no effect on the risk of nonvertebral fracture, including hip fracture.

Common adverse effects associated with raloxifene include hot flashes, peripheral edema, and leg cramps. Raloxifene carries a black box warning for increased risk of venous thromboembolism and death from stroke.

**Calcitonin Salmon.** Calcitonin works by decreasing osteoclast-mediated resorption, resulting in increased BMD and bone strength. Clinical trial data confirm its ability to reduce the relative risk of vertebral fracture by 33% to 36% over 3 years, but no effect on nonvertebral or hip fractures. Calcitonin also has an analgesic effect.
on pain associated with vertebral fracture. The approved calcitonin product, available as a nasal spray or injection solution, is a synthetic polypeptide in the same amino acid sequence found in calcitonin of salmon origin. Calcitonin nasal spray is administered intranasally, alternating nostrils daily. The most common adverse effects are rhinitis, nosebleed, and sinusitis. Rarely, mucosal ulceration may occur and necessitates discontinuation. Calcitonin injection is administered subcutaneously and can produce nausea, local injection reactions, flushing, and hypersensitive allergic reactions.

**Estrogen/Hormone Therapy.** Estrogen alone is limited to patients who are post hysterectomy. Women who have not had a hysterectomy require hormone therapy (estrogen/progestogen). The Woman’s Health Initiative demonstrated a 34% reduction in the relative risk of clinical vertebral and hip fractures and a 23% reduction in other osteoporotic fractures with estrogen/progestin over 5.2 years. Adverse effects include increased risk of breast cancer, cardiovascular disease, stroke, and thromboembolism. Estrogen/hormone therapies should be considered only after nonestrogen therapies have been ruled out, and then at the lowest possible dose and for the shortest duration. Estrogen/hormone therapies are approved for prevention, not treatment, of osteoporosis.

**Teriparatide.** Teriparatide is a recombinant parathyroid hormone composed of 34 of the 84 amino acids in human parathyroid hormone. It works by stimulating osteoblast-mediated bone formation and has demonstrated a 65% and 53% reduction in the relative risk of vertebral and nonvertebral fractures, respectively. It is indicated for postmenopausal women with osteoporosis, men with primary or hypogonadal osteoporosis, and men and women with glucocorticoid-induced osteoporosis who are at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or failure to respond or intolerance to other available therapy.

Teriparatide is approved at a dose of 20 μg/day by subcutaneous injection for a duration limited to 2 years, owing to lack of long-term data and potential risk of osteosarcoma. The occurrence of osteosarcoma in rats receiving teriparatide triggered a black box warning advising the drug to be used “only for patients for whom potential benefit outweighs potential risk.” To date, osteosarcoma secondary to teriparatide has not occurred in humans. Patients with baseline risk of osteosarcoma, such as Paget’s disease or prior skeletal radiation, should not receive teriparatide. Patients with preexisting hypercalcemia also should not receive teriparatide. Other adverse events include hypercalcemia, nausea, arthralgia, leg cramps, postural hypotension, and dizziness.

**Emerging Therapies**

Emerging therapies include new dosage forms of already approved agents, new agents within existing drug classes, and agents within new classes. Oral, nasal, and transdermal forms of teriparatide are in development, as well as a full-length recombinant parathyroid hormone. Second-generation estrogen agonist-antagonists include bazedoxifene, with and without conjugated estrogen, and lasofoxifene. Denosumab is the first drug in a new class known as RANKL inhibitors and has an application pending with the FDA for the prevention and treatment of postmenopausal osteoporosis, and for the prevention and treatment of bone loss in patients undergoing hormone ablation for either breast or prostate cancer. A human monoclonal antibody, denosumab binds to RANKL, blocking its interaction with RANK thereby inhibiting osteoclast activation and decreasing bone resorption and increasing BMD. It is administered as a subcutaneous injection twice yearly. Phase III clinical trial data have demonstrated its efficacy in reducing the relative risk of vertebral, hip, and nonvertebral fractures by 68%, 40%, and 20%, respectively, compared with placebo in postmenopausal women with osteoporosis. Head-to-head and transition studies comparing bisphosphonates and denosumab have demonstrated noninferiority to bisphosphonates in postmenopausal osteoporosis. Denosumab has documented prevention of bone loss due to aromatase inhibitors for breast cancer and gonadotropin-releasing hormone agonists for prostate cancer.

Odanacatib, now in phase III testing, is a monoclonal antibody that inhibits cathepsin K. A phase II study showed it increased lumbar spine and hip BMD in postmenopausal women with low BMD. Other new drug classes under development for osteoporosis are listed in Table 3.

**Patient Education**

Response to therapy depends on patients taking their medication exactly as prescribed in terms of timing, method, and dosage. Patient education should focus on ensuring patients have full understanding of these expectations. Table 4 lists agent-specific key points to be included in a patient education program. For all agents, potential adverse events should be described, as well as any action to take should the patient experience them.

**Adherence.** Good adherence is essential for response to osteoporosis therapy and should be a major focus of patient education. A meta-analysis of 17 randomized and observation trials revealed after 1 year, only 47% of patients are compliant with osteoporosis therapy (taken when and as prescribed) and 42% are persistent (taken for duration). These figures demonstrated the extent of the adherence problem (compliance plus persistence) to osteoporosis therapy. Data from another study suggested patients who take less than 50% of doses do not have a significant frac-
Table 4. Agent-Specific Key Points to Cover in Patient Education

<table>
<thead>
<tr>
<th>Agent</th>
<th>Patient Education Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates, oral</td>
<td>• Take the medication at the dose and time prescribed</td>
</tr>
<tr>
<td></td>
<td>• Take medication on empty stomach before breakfast or coffee</td>
</tr>
<tr>
<td></td>
<td>• Take with a full glass of water only</td>
</tr>
<tr>
<td></td>
<td>• Stay upright, sitting or standing, for 30 minutes (alendronate, risedronate) or 60 minutes (ibandronate)</td>
</tr>
<tr>
<td></td>
<td>• Take other medications later</td>
</tr>
<tr>
<td></td>
<td>• Report any difficulty swallowing or gastrointestinal pain</td>
</tr>
<tr>
<td></td>
<td>• Instruction on missed dose</td>
</tr>
<tr>
<td>Bisphosphonates, oral and intravenous</td>
<td>• Practice good oral hygiene and tell health care provider if invasive dental work planned</td>
</tr>
<tr>
<td></td>
<td>• Report any musculoskeletal pain</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>• Take with or without food, any time of day, but best to take same time each day</td>
</tr>
<tr>
<td></td>
<td>• Educate about signs and symptoms of blood clots</td>
</tr>
<tr>
<td></td>
<td>• Instruction on missed dose</td>
</tr>
<tr>
<td>Calcitonin salmon, spray</td>
<td>• Store unopened bottles in refrigerator</td>
</tr>
<tr>
<td></td>
<td>• Bring bottle to room temperature, assemble, and prime pump before first use only</td>
</tr>
<tr>
<td></td>
<td>• Opened bottle is good for 35 days</td>
</tr>
<tr>
<td></td>
<td>• Alternate nares daily</td>
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<tr>
<td></td>
<td>• Instruction on missed dose</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>• Proper injection technique</td>
</tr>
<tr>
<td></td>
<td>• Administer into thigh or abdominal wall</td>
</tr>
<tr>
<td></td>
<td>• Pen contains 28 doses</td>
</tr>
<tr>
<td></td>
<td>• Educate on needle disposal</td>
</tr>
<tr>
<td></td>
<td>• Keep in refrigerator; do not freeze</td>
</tr>
<tr>
<td></td>
<td>• Orthostatic hypotension is more common with first few doses</td>
</tr>
<tr>
<td></td>
<td>• Instruction on missed dose</td>
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</tbody>
</table>

Case 2. Glucocorticoid-Induced Osteoporosis

Marge is a 70-year-old white woman with a history of rheumatoid arthritis and hyperlipidemia. At a height of 5 feet 2 inches, she is overweight at 142 lb. She does not smoke and drinks three glasses of wine per week. Her current medications include methotrexate, prednisone (doses ranging up to 7.5 mg daily for the last year), atorvastatin, and a multivitamin. Her 25(OH)D serum concentration is 22 ng/mL. She recently had a DXA scan performed and her T-scores were −1.2 lumbar spine; −1.4 right femoral neck; and −1.3 right total hip.

Questions to Ask About This Case
• What is the pathogenesis of glucocorticoid-induced osteoporosis?
• What treatment guidelines are relevant to this case?

Pathogenesis of Glucocorticoid-Induced Osteoporosis

Glucocorticoids decrease the number of osteoblasts, thereby reducing their activity, while also increasing the rate of osteoclast-mediated resorption. Calcium homeostasis may be altered with reduced absorption and increased excretion, and sex hormone production may be reduced. The result is significant loss of BMD, with drops of 3% to 27%, especially during the first 6 to 12 months of glucocorticoid therapy. Trabecular bone is primarily affected, followed by cortical bone, compromising both bone quality and quantity thereby increasing fracture risk.71,72

Treatment Guidelines for Glucocorticoid-Induced Osteoporosis

Guidelines from the American College of Rheumatology on prevention of glucocorticoid-induced osteoporosis recommend a bone-healthy lifestyle, including calcium and vitamin D supplementation.73 It is also reasonable for pharmacists to consider alternative medications that may allow for management of the disease while reducing steroid doses or avoiding steroids. Bisphosphonate therapy is recommended to help reduce bone loss and maintain mass in all men and postmenopausal women starting long-term (3 months or more) glucocorticoid treatment at 5 mg or more per day (or prednisone equivalent). Alternatively, bisphosphonates may be initiated after BMD testing shows a T-score of less than −1. Alendronate, risedronate, and zoledronic acid have data in the setting of glucocorticoid-induced osteoporosis and are approved treatment options.22,24,28,74-76 Teriparatide also has data and is approved for this indication.32,77

Stop & Think
What care plan would you develop for Marge?

The Role of the Pharmacist in Managing Osteoporosis

Pharmacists can take advantage of opportunities for preventive or therapeutic intervention when patients present with new prescriptions or request refills. They also can create opportunities for intervention by planning awareness events for the community, reaching out to primary care providers about specific risk groups in their patient populations, or establishing osteoporosis screening or management services.

Advocate Bone-Healthy Lifestyle.
Pharmacists should educate their patients about universal lifestyle modifications.
appropriate for everyone. Most individu-
als need calcium and vitamin D supple-
mentation, but the choices are confusing.
Pharmacists can help patients select the
appropriate product and dose. This
preventive service can be extended to
younger individuals who are still build-
ing or maintaining their peak bone mass.

**Identify At-Risk Individuals.** By
knowing which medications and con-
ditions have adverse skeletal effects, phar-
macists can identify individuals at risk
and counsel them about appropriate
lifestyle modifications, alternative medica-
tions, and osteoporosis pre-
vention and treatment. For example,
heel ultrasounds can be offered as an
initial screening for low bone mass.
The online FRAX tool can be used to
calculate fracture risk. A patient’s refill
history can be used to identify patients
on long-term glucocorticoids who are
at risk of glucocorticoid-induced osteo-
porosis. In all cases, those at risk can
be referred to their primary care pro-
viders for further evaluation.

**Facilitate Treatment.** Pharmacists
should educate their patients about the
correct way to take prescribed medica-
tion and the potential adverse effects.
For expensive regimens, pharmacists
may facilitate third-party authoriza-
tions prior to patients starting therapy.
Pharmacists also can help identify and
resolve medication-related adverse
events.

**Promote Adherence.** Follow-up
phone calls, refill monitoring, educa-
tion, adherence tools and reminders, and
adverse effect counseling are some ways
pharmacists can encourage good
adherence in their patients being treated
for osteoporosis. As needed, pharma-
cists can consult with the prescriber to
identify alternative routes of administra-
tion or therapies.

All of these interventions may be
incorporated into pharmacy mediation
therapy management (MTM) services. In
addition, they may be integrated in
a pharmacist-run osteoporosis service
financed through patient payments and
third-party reimbursement.70-81

**Conclusion**

Osteoporosis contributes signifi-
cantly to morbidity and mortality, particularly
among elderly persons. Pharmacists
are key to helping resolve this major
government health threat through preventive
measures and facilitating treatment of
those affected. Opportunities exist for
pharmacists to assist patients with phar-
macologic and nonpharmacologic strat-
egies to address osteoporosis through
new or existing services within their
patient populations.

### Reality Check

List the ways in which osteoporosis services can be integrated into your pharmacy’s MTM services.

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New Approaches to the Management of Osteoporosis

Instructions: The assessment questions printed below allow you to preview the online CPE exam. Please review all of your answers to be sure you have marked the proper letter on the online CPE exam. There is only one correct answer to each question.

1. The rate of osteoporosis is lowest in which of the following groups?
   
   a. Black.
   b. White.
   c. Asian.
   d. Hispanic.

2. Which of the following statements about hip fracture is true?
   
   a. A hip fracture increases the risk of mortality within 1 year by up to 25%.
   b. One half of patients with hip fracture will require long-term care.
   c. One quarter of patients with hip fracture will experience long-term decreases of mobility.
   d. One third of patients with hip fracture require hospitalization.

3. Which of the following cell types mediate bone resorption?
   
   a. Osteoblast.
   b. Osteoclast.
   c. Osteocyte.
   d. Both a and b.

4. RANKL, released by _____, binds to RANK on mature _____, triggering bone _____.
   
   a. Osteoblasts, osteoclasts, resorption.
   b. Osteoclasts, osteoblasts, resorption.
   c. Osteoblasts, osteoclasts, formation.
   d. Osteoclasts, osteoblasts, formation.

5. Primary osteoporosis is primarily due to the effects of:
   
   a. Estrogen deficiency only.
   b. Multiple disorders that adversely affect the skeleton.
   c. Aging and estrogen deficiency.
   d. Genetic osteoblast dysfunction.

6. Which of the following can be used to diagnose osteoporosis?
   
   a. BMD by DXA.
   b. Heel ultrasound.
   c. FRAX.
   d. All of the above.

7. FRAX can be used to calculate fracture risk in which of the following patients?
   
   a. A premenopausal woman with a family history of osteoporotic fracture.
   b. A postmenopausal woman without access to BMD testing by DXA.
   c. A 75-year-old woman currently receiving bisphosphonate therapy.
   d. A 48-year-old man on long-term oral glucocorticoid therapy.

8. Which of the following is a fracture risk factor used in the FRAX tool?
   
   a. Smoking, past and current.
   b. Inhaled steroid for asthma.
   c. Fragility fracture in sibling.
   d. Three or more alcoholic drinks daily.

9. A patient on a daily proton pump inhibitor may have difficulty disintegrating or dissolving:
   
   a. Calcium carbonate.
   b. Calcium citrate.
   c. Calcium carbonate and calcium citrate.
   d. Neither calcium carbonate nor calcium citrate.

10. The optimal serum 25(OH)D concentration is _____ or higher.
   
   a. 20 ng/mL.
   b. 30 ng/mL.
   c. 50 ng/mL.
   d. 75 ng/mL.

11. Osteopenic individuals with a _____ or greater 10-year probability of hip fracture and a _____ or greater 10-year probability of major osteoporotic fracture should be considered for pharmacologic treatment.
   
   a. 10%; 15%.
   b. 20%; 3%.
   c. 3%; 20%.
   d. 20%; 20%.

12. Oral bisphosphonates reduce the relative risk of vertebral fracture in the range of:
   
   a. 30% to 40%.
   b. 40% to 50%.
   c. 40% to 75%.
   d. 75% to 85%.
13. A patient reports that she doesn’t always take her oral risedronate because of mild abdominal discomfort. The pharmacist should:
   a. Suggest she take it with a meal.
   b. Tell her to discontinue immediately.
   c. Explain the need for good adherence and tell her to stick with it despite the discomfort.
   d. First ask her if she is staying upright for at least 30 minutes after swallowing the tablet.

14. Which of the following statements about ONJ is true?
   a. A causal relationship between ONJ and oral, but not intravenous, bisphosphonates has been established.
   b. ONJ does not occur in the general population.
   c. Tooth extraction is a risk factor.
   d. ONJ is more common in patients taking bisphosphonates for osteoporosis than for multiple myeloma.

15. Which of the following agents should be recommended for a 70-year-old woman with osteoporosis of the spine, back pain, and severe renal insufficiency (CrCl 10 mL/min)?
   a. Calcitonin salmon, intranasal.
   b. Ibandronate, intravenous.
   c. Alendronate, oral.
   d. Zoledronic acid, intravenous.

16. Which of the following statements about estrogen/hormone therapy for osteoporosis is true?
   a. It is approved for the prevention, but not treatment, of osteoporosis.
   b. It should be used alone (without progestogen) only in women who have not had a hysterectomy.
   c. Data from the Woman’s Health Initiative demonstrated a reduction in vertebral fracture relative risk only.
   d. It should be tried before nonestrogen therapies.

17. Which of the following is the only approved agent with a direct effect on osteoblasts?
   a. Estrogen/hormone therapy.
   b. Denosumab.
   c. Calcitonin salmon.
   d. Teriparatide.

18. Which of the following agents carries a black box warning for osteosarcoma?
   a. Raloxifene.
   b. Calcitonin salmon.
   c. Teriparatide.
   d. Zoledronic acid.

19. Which of the following emerging agents directly blocks the interaction of RANKL and RANK?
   a. Denosumab.
   b. Lasofoxifene.
   c. Intranasal teriparatide.
   d. Bazedoxifene.

20. Therapy for glucocorticoid-induced osteoporosis should be considered:
   a. After BMD testing shows a T-score of less than –1.
   b. At initiation of long-term (≥3 months) glucocorticoid therapy at a dose of 5 mg prednisone (or equivalent) or more.
   c. In patients on long-term inhaled glucocorticoids.
   d. Both a and b.

CPE Instructions
Completing a posttest at www.pharmacist.com/education is as easy as 1-2-3...

1. Go to Online CPE Quick List and click on the title of this activity.
2. Log in. APhA members enter your user name and password. Not an APhA member? Just click “Create one now” to open an account. No fee is required to register.
3. Successfully complete the CPE exam and evaluation form to gain immediate access to your Statement of Credit.

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