Promoting bone health: Focus on postmenopausal women and patients receiving systemic therapy for breast or prostate cancer
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S2 Introduction
Eric J. MacLaughlin

S4 Improving osteoporosis screening, risk assessment, diagnosis, and treatment initiation: Role of the health-system pharmacist in closing the gap
Eric J. MacLaughlin

S9 Managing osteoporosis in postmenopausal women
Sheryl F. Vondracek

S20 Managing cancer treatment-induced bone loss and osteoporosis in patients with breast or prostate cancer
Laura Boehnke Michaud

S31 Continuing education

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See page S31 or http://ce.ashp.org to locate the continuing-education learning objectives, self-assessment questions, and instructions covering the articles in this supplement.
Promoting bone health: Focus on postmenopausal women and patients receiving systemic therapy for breast or prostate cancer

Introduction

ERIC J. MACLAUGHLIN

Osteoporosis, a disease characterized by low bone mass, deterioration of bone structure, and increased susceptibility to fractures, is a major public health threat in the United States. In 2005, more than 2 million fractures were attributed to osteoporosis. Advanced age is one of many risk factors for the disease; 55% of Americans 50 years of age and older are affected. The impact of osteoporosis is expected to increase in the future because of the graying of America; the annual number of fractures caused by osteoporosis is expected to exceed 3 million by year 2025.

The morbidity, mortality, and costs associated with osteoporosis-related fractures are considerable. The costs of osteoporosis-related fractures amounted to an estimated $19 billion in 2005 and are projected to increase to more than $25 billion by 2025.1

Osteoporosis and osteoporosis-related fractures are much more common in women than in men; postmenopausal women are particularly at risk because of the reduction in ovarian estrogen production that accompanies menopause.1 Most cases of osteoporosis occur in postmenopausal women,2 and the number of cases is expected to grow as the baby boom generation ages.

Patients with breast or prostate cancer who are receiving hormone-ablation therapy or other systemic therapies may be at increased risk for osteoporosis and fractures. Nearly 1.5 million new cases of cancer were expected to be diagnosed in 2009, and breast cancer and prostate cancer are the most commonly diagnosed malignancies in women and men, respectively.3 Most clinicians are vigilant for osteoporosis in postmenopausal women. Elderly men and patients who receive hormone-ablation therapy for breast or prostate cancer are less obvious groups that also should be screened for the disease. Health-system pharmacists can play an important role in identifying patients with osteoporosis or bone loss and recommending interventions to improve bone health.

The first article in this supplement provides an overview of the epidemiology of osteoporosis and related fractures in the United States, morbidity and mortality from the disease, the gap between evidence and practice regarding
screening and treatment, fracture risk assessment, diagnosis, and indications for treatment to reduce fracture risk. In the second article, strategies used in managing postmenopausal osteoporosis, including a bone-healthy lifestyle, adequate calcium and vitamin D intake are discussed. Various drug therapies for osteoporosis prevention and treatment, and considerations in selecting osteoporosis drug therapy are also reviewed.

Finally, the third article addresses the rationale for monitoring bone health in patients with breast or prostate cancer who are receiving hormone-ablation or other systemic therapy, national guidelines for screening for and treatment of bone loss and osteoporosis in patients with these malignancies, and current and emerging therapeutic options for managing bone loss and osteoporosis in patients with breast or prostate cancer. The role of health-system pharmacists in promoting bone health in postmenopausal women and in patients with breast or prostate cancer is described in the second and in the third article, respectively.

References
Improving osteoporosis screening, risk assessment, diagnosis, and treatment initiation: Role of the health-system pharmacist in closing the gap

ERIC J. MACLAUGHLIN

A n estimated 10 million Americans have osteoporosis, and another 34 million people in the United States have osteopenia (i.e., low bone mass that is less severe than that associated with osteoporosis), which increases the risk for osteoporosis. Osteoporosis has a disproportionate effect on women; 80% of Americans with osteoporosis are women and 20% are men. One in two women and one in four men older than 50 years of age will experience an osteoporosis-related fracture in their remaining lifetime.

Osteoporosis is a significant health concern because of increased risk of fractures and the resultant morbidity and mortality. Of the more than 2 million osteoporosis-related fractures in the United States in 2005, 547,000 were vertebral fractures, 397,000 were wrist fractures, 297,000 were hip fractures, 135,000 were pelvic fractures, and 675,000 fractures occurred at other sites. Osteoporotic fractures can lead to chronic, disabling pain. Compression fractures of the vertebrae may lead to kyphosis (curvature of the thoracic region of the spine), diminished pulmonary function, and gastrointestinal complications. Impaired health-related quality of life resulting in depression is another possible consequence of osteoporosis-related fractures. Nursing home placement may be required, especially after hip fracture.

Hip fractures are one of the most devastating consequences of osteoporosis.
It is estimated that approximately one in five patients 50 years of age or older with hip fracture will die within one year after the fracture. Roughly 20% of patients who were ambulatory before a hip fracture require long-term care afterward. Only 15% of patients with hip fractures can walk unaided six months after the fracture. The rate of hip fractures is two to three times higher in women than in men, but the one-year mortality rate is twice as high in men than in women. Thus, although osteoporosis tends to be thought of as a woman’s disease because of its higher prevalence in women than in men, its impact is great in both sexes.

Closing the gap

Although there is ample evidence of the need for and benefits of screening for osteoporosis to prevent morbidity and mortality, this evidence often does not translate into practice. Many patients with or at risk for osteoporosis are not educated on the steps they can take to prevent or minimize its impact on health. It is estimated that only 5% to 50% of women with fragility fractures (i.e., fractures after a fall from standing height or lower, with minimal trauma) are screened and treated for osteoporosis. Many patients are not treated even after receiving a formal diagnosis.

Several bone health initiatives have been developed to fill this gap between evidence and practice. Own the Bone is a Web-based quality improvement program (www.aoassn.org/OwnTheBone.asp) designed by the American Orthopaedic Association to improve the use of evidence-based strategies for preventing secondary fractures after fragility fractures. In a 10-month pilot project using this program, patient counseling on calcium and vitamin D supplementation, weight-bearing exercise, smoking cessation, and fall prevention significantly improved after implementation of the program, compared with the period before program implementation ($p < 0.0001$). The use of referral letters to physicians recommending evaluation and treatment of a patient’s fracture and letters to patients recommending that they see a physician for evaluation and treatment of osteoporosis associated with the fracture also improved significantly after program implementation ($p < 0.0001$). However, the use of bone mineral density (BMD) testing and pharmacotherapy to prevent or treat osteoporosis did not improve and remained low after program implementation (11% for BMD testing and 5% for pharmacotherapy). Thus, although the Own the Bone initiative has improved care in many areas, there is still considerable room for improvement.

Risk factors

A wide variety of factors (Table 1) increase the risk for osteoporosis and fractures. Ascertain lifestyle, genetics, the presence of certain diseases, and the use of certain medications is part of the risk-assessment process.

Several clinical factors affect the risk for hip fracture independent of osteoporosis. In addition, the prevention and management of osteoporosis have been examined at a national level from a quality of care standpoint. Health-system pharmacists can play a vital role in closing the gap between evidence and practice by collaborating with physicians and other health care professionals to ensure that patients are screened and treated as appropriate for osteoporosis.

### Table 1

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Osteoporosis and Fractures in Postmenopausal Women and Men Age 50 and Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle</td>
<td>Low calcium intake&lt;br&gt;Vitamin D insufficiency&lt;br&gt;Excessive vitamin A intake&lt;br&gt;High caffeine intake&lt;br&gt;High salt intake&lt;br&gt;Inadequate physical activity, especially weight-bearing exercise&lt;br&gt;Immobilization&lt;br&gt;Cigarette smoking (active or passive)&lt;br&gt;Alcohol intake $\geq 3$ drinks/day&lt;br&gt;Falling&lt;br&gt;Low body mass index</td>
</tr>
<tr>
<td>Genetics</td>
<td>Cystic fibrosis, parental history of hip fracture&lt;br&gt;Hypogonadal states (e.g., premature ovarian failure)&lt;br&gt;Endocrine disorders (e.g., diabetes mellitus, thyrotoxicosis)&lt;br&gt;Gastrointestinal disorders (e.g., malabsorption)&lt;br&gt;Hematologic disorders (e.g., leukemias, lymphomas, sickle cell disease)&lt;br&gt;Rheumatic and autoimmune diseases (e.g., lupus, rheumatoid arthritis)</td>
</tr>
<tr>
<td>Medications</td>
<td>Cancer chemotherapy&lt;br&gt;Aromatase inhibitors&lt;br&gt;Luteinizing hormone releasing hormone (gonadotropin releasing hormone) agonists&lt;br&gt;Corticosteroids&lt;br&gt;Aluminum-containing antacids</td>
</tr>
</tbody>
</table>

This list includes common risk factors and is not inclusive.
of BMD. A body mass index (BMI) of 20 kg/m² (reflecting thinness) increases the risk for hip fracture nearly twofold compared with a BMI of 25 kg/m². A BMI of 30 kg/m² (considered obese) slightly reduces the risk for hip fracture compared with a BMI of 25 kg/m². "Ever" use of corticosteroids and parental history of hip fracture more than double the risk for hip fracture. Current smoking or prior fracture after the age of 50 increases the risk for hip fracture, although not to the same extent as corticosteroid use or parental history of hip fracture. Consumption of more than two alcoholic beverages daily also increases the risk for hip fracture.

### Diagnosis

The World Health Organization (WHO) has established diagnostic criteria for osteoporosis (Table 2) in postmenopausal women and men more than 50 years of age as measured by central dual-energy X-ray absorptiometry (DXA) of the spine, hip, or forearm. These criteria are based on the T-score, which reflects the difference between the patient’s BMD and the expected value for a “young, normal” adult of the same sex, expressed as the number of standard deviations below or above the mean on a normal distribution curve. A young adult is the basis for comparison because this is the age at which bone mass typically reaches a peak. A T-score of –2.5 or lower (i.e., 2.5 or more standard deviations below the expected BMD) is considered osteoporosis. Osteoporosis is considered severe if the T-score is –2.5 or lower and there is evidence of fractures. A T-score of –1.0 to –2.5 (i.e., 1.0 to 2.5 standard deviations below the expected BMD for a young, normal adult of the same sex) is considered osteopenia. A T-score of –1.0 or higher (i.e., a BMD above or within 1 standard deviation lower than that expected) is considered normal.

The T-score is predictive of fracture risk, but it is not the only risk factor. Advanced age is an independent risk factor for osteoporotic fractures. In women between the ages of 50 years and 80 years, the 10-year risk for osteoporotic fractures is higher for older women than for younger women with the same T-score (Figure 1).

The use of T-scores to predict fracture risk has several other limitations. The BMD on which the T-score is based accounts for 60% to 70% of the variation in bone strength. Factors that account for the other 30% to 40% of variation in bone strength are unclear. Some of the clinical risk factors listed in Table 1 likely play important roles in bone strength that are not accounted for in T-scores. In addition, BMD measured at one site (e.g., femoral neck, or hip) does not necessarily reflect the BMD at another site (e.g., vertebrae, or spine). Also, T-scores do not provide information about the absolute risk of fracture because they are based on a measure of BMD relative to a population of young, normal adults. Thus, the T-score alone should not be relied on to predict the risk for osteoporosis-related fractures.

### Screening and treatment decisions

Assessing the risk for osteoporotic fractures and determining when to initiate treatment to reduce fracture risk pose challenges for clinicians. To
address these challenges, the National Osteoporosis Foundation (NOF), the leading volunteer organization in the United States solely dedicated to the problem of osteoporosis and promoting bone health, began publishing a Clinician’s Guide to Prevention and Treatment of Osteoporosis in 1999. This publication, which provides guidelines for osteoporosis prevention, risk assessment, diagnosis, and treatment in postmenopausal women and men age 50 and older, was updated in 2008.

According to the NOF, women 65 years of age or older and men 70 years of age or older should undergo BMD testing regardless of the presence of clinical risk factors. Postmenopausal women and men 50–69 years of age with risk factors also should be tested. Testing is recommended to assess disease in postmenopausal women and men older than 50 years of age who have had a fracture. DXA testing may also be indicated in other populations, including children and adolescents, that may be at significant risk of fracture, but detailed discussion of these special populations is beyond the scope of this article.

The most recent (2008) update to the Clinician’s Guide to Prevention and Treatment of Osteoporosis incorporates an automated fracture risk assessment tool known as FRAX that is available online (www.shef.ac.uk/FRAX/) from the WHO. The FRAX tool takes into consideration many of the risk factors listed in Table 1, including age (40–90 years), sex, weight, height, previous fracture, parental history of hip fracture, current smoking, ever corticosteroid use (prednisolone ≥5 mg/day or equivalent for longer than three months), rheumatoid arthritis, secondary osteoporosis (e.g., caused by several diseases listed in Table 1), consumption of three or more alcoholic beverages daily, and femoral neck (or total hip) BMD measured using one of several possible devices.

The FRAX tool may be used regardless of whether BMD information is available. This feature is helpful for areas of the country where BMD testing with DXA is not readily available (e.g., rural towns). The FRAX tool calculates the 10-year probability of major osteoporotic fracture and the 10-year probability of hip fracture in previously untreated patients. These probabilities are analogous to the 10-year risk for coronary heart disease calculated with an online tool based on the Framingham Heart Study. Separate FRAX tools are available for Caucasian, black, Hispanic, and Asian residents of the United States, as well as residents of several different countries.

The Clinician’s Guide to Prevention and Treatment of Osteoporosis lists criteria for initiating treatment to reduce fracture risk (Table 3), with threshold values for T-scores and fracture probabilities calculated using the FRAX tool (i.e., treatment should be initiated when the T-score, probability of fracture, or both exceeds the threshold). These criteria and the FRAX tool can be used as the basis for treatment decisions. The thresholds for fracture probabilities calculated with the FRAX tool are particularly valuable for making treatment decisions for patients with osteopenia. The thresholds established by the NOF are based in part on a cost-effectiveness analysis of treatments. In patients with osteopenia, treatment is recommended if the 10-year probability of hip fracture is ≥3% or if the 10-year probability of a major osteoporosis-related fracture is ≥20%.

Although the fracture probabilities calculated with FRAX can guide treatment recommendations, clinician judgment, patient preference, or both may enter into treatment decisions regardless of whether thresholds are exceeded. For example, treatment may be initiated in a patient with osteopenia and a 10-year probability of a hip fracture of only 2% (i.e., below the 3% threshold established by the NOF) because of significant patient concerns about a sibling with a hip fracture.

Conclusion

Osteoporosis causes considerable morbidity and mortality. Rates of screening for and treatment of osteoporosis are inadequate despite ample evidence of the potential benefits. Various initiatives have been developed to address the situation and improve patient outcomes. The release of the NOF Clinician’s Guide to Prevention and Treatment of Osteoporosis incorporating the FRAX fracture risk assessment tool will facilitate risk assessment and treatment decisions. Health-system pharmacists can help improve patient outcomes by using these tools and collaborating with physicians and other members of the health care team in osteoporosis screening, risk assessment, diagnosis, and treatment efforts.

Table 3. National Osteoporosis Foundation Recommendations for Initiation of Treatment to Reduce Fracture Risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Fracture Probability</th>
</tr>
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<tbody>
<tr>
<td>A hip or vertebral</td>
<td>≥3%</td>
</tr>
<tr>
<td>(clinical or morphometric)</td>
<td></td>
</tr>
<tr>
<td>T-score ≤ -2.5 at the femoral</td>
<td>≥3%</td>
</tr>
<tr>
<td>neck or spine after evaluation</td>
<td></td>
</tr>
<tr>
<td>of appropriate secondary</td>
<td></td>
</tr>
<tr>
<td>causes</td>
<td></td>
</tr>
<tr>
<td>Osteopenia (T-score between -1.0</td>
<td>≥3%</td>
</tr>
<tr>
<td>and -2.5 at the femoral neck</td>
<td></td>
</tr>
<tr>
<td>or spine)</td>
<td></td>
</tr>
<tr>
<td>10-year probability of a hip</td>
<td>≥3% or 10-year</td>
</tr>
<tr>
<td>fracture ≥ 3%</td>
<td></td>
</tr>
<tr>
<td>probability of a major</td>
<td></td>
</tr>
<tr>
<td>osteoporosis-related fracture ≥</td>
<td>≥20%</td>
</tr>
<tr>
<td>20% based on the FRAX tool</td>
<td></td>
</tr>
</tbody>
</table>

*Clinician judgment, patient preference, or both may enter into treatment decisions regardless of whether thresholds are exceeded.*
**Symposium**

**Health-system pharmacist**

**References**


Managing osteoporosis in postmenopausal women

SHERYL F. VONDRACEK

Purpose. To describe strategies used in managing postmenopausal osteoporosis, including a bone-healthy lifestyle, adequate calcium and vitamin D intake, and drug therapy options; considerations in selecting osteoporosis drug therapy; and the role of health-system pharmacists in managing osteoporosis in postmenopausal women.

Summary. Postmenopausal women are at risk for osteoporosis and fractures. Weight-bearing and resistance exercise, limiting alcohol and caffeine intake, smoking cessation, and fall prevention strategies are part of a bone-healthy lifestyle used to manage postmenopausal osteoporosis. Supplements containing calcium and vitamin D are needed by many postmenopausal women because of an inadequate intake and other factors. The choice of osteoporosis drug therapy should take into consideration patient characteristics and preference and drug efficacy, safety, route of administration, dosing frequency, convenience, cost, and potential for nonadherence. Bisphosphonates generally are preferred for the prevention and treatment of osteoporosis in postmenopausal women, with raloxifene, teriparatide, and calcitonin salmon as alternatives. Denosumab, a fully human monoclonal immunoglobulin G2 antibody, may become available soon for prevention and treatment of postmenopausal osteoporosis. Health-system pharmacists can improve the management of osteoporosis in postmenopausal women by counseling them on a bone-healthy lifestyle and making recommendations for calcium and vitamin D supplements and osteoporosis medications to prevent or treat the disease.

Conclusion. A variety of approaches are available to promote bone health in postmenopausal women. Health-system pharmacists can promote interventions to optimize patient outcomes.

Index terms: Antibodies; Bisphosphonates; Calcitonin salmon; Calcium; Denosumab; Estrogen agonist-antagonists; Fractures; Hormones; Minerals; Osteoporosis; Pharmacists, hospital; Postmenopause; Raloxifene; Teriparatide; Vitamin D; Vitamins; Women


Peak bone mass is achieved at 18–25 years of age, after which time bone loss occurs. The prevention of osteoporosis starts in early childhood through early adulthood, with the goal of optimizing bone development and peak bone mass. Menopause is accompanied by an accelerated rate of bone loss due to a decrease in estrogen levels and an increase in bone resorption, resulting in weakening of bones. Osteoporosis or osteopenia (low bone mass that is less severe than that associated with osteoporosis) and fractures are common consequences of this accelerated bone loss in postmenopausal women. Once women reach menopause, the goal is to minimize this accelerated bone loss. In postmenopausal women with osteoporosis or osteopenia, interventions to maintain or increase bone mass and strength and prevent fractures are key. In postmenopausal women with fractures caused by osteoporosis, the goals of treatment are to prevent additional fractures, improve functional capacity, minimize pain and deformity, and improve quality of life.

A bone-healthy lifestyle and adequate calcium and vitamin D intake play important roles in managing osteoporosis in postmenopausal women. Various drug therapies are used to prevent and treat the disease in this patient population.

Bone-healthy lifestyle

Physical activity is an important component of a bone-healthy lifestyle. Exercise can strengthen bones and decrease the risk of falls and fractures by improving muscle strength, coordination, balance, and mobility.

According to the U.S. Department of Health and Human Services 2008

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Physical Activity Guidelines for Americans, adults should perform at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity every week. Weight-bearing exercises (e.g., walking, jogging, stair climbing) strengthen bones by stimulating bone deposition and are best for bone health. Bicycling and swimming are aerobic and provide cardiovascular benefits, but they are not considered weight bearing. Incorporation of resistance exercises (e.g., the use of free weights, weight machines, or elastic bands) at least twice a week is also recommended to strengthen muscles and improve bone health. Older adults should be as physically active as their abilities and health conditions permit.

Limiting alcohol and caffeine intake is part of a bone-healthy lifestyle. Excessive consumption of alcohol (three or more drinks per day) adversely affects bone health and increases the risk of falls. Daily intake of alcoholic beverages should not exceed one drink for women or two drinks for men.

Limiting caffeine intake promotes bone health because caffeine increases urinary calcium excretion. A high caffeine intake (the equivalent of four or more cups of coffee daily) increases the risk for osteoporosis and fractures in women with a low calcium intake (<700 mg/day). Several cups of caffeinated beverages may be consumed daily if calcium intake is adequate. For most postmenopausal women who have an inadequate calcium intake, caffeine intake should be limited to two servings or less per day to avoid excessive urinary calcium loss.

Smoking avoidance or cessation is also important for a bone-healthy lifestyle, as cigarette smoking is an independent risk factor for osteoporotic fractures.

Fall prevention strategies are an important component of a bone-healthy lifestyle for patients with osteoporosis because falls are a major cause of fractures in these patients. These strategies include avoiding unnecessary use of medications that can increase the risk of falls (e.g., benzodiazepines; other anxiolytics, sedatives, and hypnotics; antidepressants; antipsychotic agents; opioid analgesics), getting a vision checkup, and conducting a personal and home safety check. A brochure and booklet with safety checklists are available from the Centers for Disease Control and Prevention. Table 1 lists items on these checklists.

Calcium
The National Osteoporosis Foundation (NOF) recommends a daily elemental calcium consumption through diet or calcium supplements of at least 1000 mg for men and women 19–49 years of age and at least 1200 mg for men and women 50 years of age or older. Most postmenopausal women fall into the latter age group and require at least 1200 mg/day. The safe upper limit for total daily calcium intake from all sources is 2500 mg. Increasing daily calcium intake beyond 1200–1500 mg is of limited benefit, and it may increase the risk for kidney stones and cardiovascular disease.

Many postmenopausal women do not obtain sufficient calcium in their diets. The average daily dietary calcium intake in women 60 years of age or older is only 660 mg (i.e., roughly half the recommended amount).

Diet is the preferred source of calcium, although supplements may be used when dietary calcium is inadequate. Fat-free or low-fat dairy products are a good source of calcium. Calcium-fortified fruit juices, breakfast cereals, breads, soy milk, and bottled water are alternatives.

Information about the calcium content of a serving is provided on the Nutrition Facts label on food products. This information can be confusing to patients because the calcium content is expressed as a percentage of a 1000-mg/day intake of calcium. The amount of elemental calcium in a serving can be calculated by multiplying the percentage figure by 10. For example, an 8-oz serving of fat-free milk with a 30% calcium content contains 300 mg of elemental calcium.

Various calcium salts are available. The two most commonly used salts, calcium carbonate and calcium citrate, differ in their elemental calcium content, formulations, cost, requirements for administration with food, potential for certain drug interactions, and tolerability. Calcium carbonate is 40% elemental calcium by weight, and calcium citrate is 21%
elemental calcium.6 Labels on calcium supplements now express the strength as elemental calcium instead of or in addition to the salt, minimizing the need for conversion of calcium salt content to elemental calcium content, which can cause confusion.

A wide variety of calcium carbonate dosage forms and formulations are available, including flavored soft chews and tablets that dissolve in the mouth or are chewable. Many products are inexpensive. By contrast, a smaller variety of calcium citrate formulations are available, and they tend to be more expensive than calcium carbonate products.

The quality of calcium supplements varies, and some products may not dissolve properly, which affects absorption.10 Others may contain lead and other toxic metals.10 The presence of the U.S. Pharmacopeia (USP) verified mark on the product label provides assurance that the product has been tested and meets USP criteria for potency, purity, dissolution, and manufacturing.12 The USP dietary supplement verification program is voluntary, so the absence of the USP verified mark on a label does not necessarily mean that the product is inferior.10

The absorption of calcium is limited, and absorption is greatest when single doses of 500–600 mg of elemental calcium or less are used.10 Thus, divided doses are recommended to meet daily calcium requirements.

Gastric acid optimizes the absorption of calcium carbonate, so it is best taken with food (food stimulates gastric acid secretion).5 Calcium citrate does not require gastric acid for absorption, so it may be taken with or without food. Calcium citrate may be preferred over calcium carbonate for patients taking acid-suppressing therapies (e.g., proton pump inhibitors) and elderly patients who typically have diminished gastric acid secretion.5 Both calcium carbonate and calcium citrate interact with many medications (e.g., tetracyclines, iron supplements, thyroid hormones).10

Adverse effects from calcium supplements include gastrointestinal (GI) upset, bloating, gas, and constipation.5 These effects may be minimized by taking the supplement in divided doses or with food or switching to another product or calcium salt.6,10 Calcium citrate may be less likely to cause these problems than calcium carbonate.2

Vitamin D

Vitamin D often is referred to as the sunshine vitamin because it is produced in the body after exposure to sunlight. Adequate levels of vitamin D are needed for GI absorption of calcium.13 Vitamin D has been in the news because of evidence that a much higher intake is needed to prevent vitamin D deficiency than was previously thought, and low levels of vitamin D appear to be linked not only to adverse effects on bone, but also to other adverse health consequences.14

Ultraviolet B light converts 7-dehydrocholesterol in the skin to cholecalciferol (vitamin D3), which undergoes hydroxylation in a two-step process to 25-hydroxycholecalciferol (25-hydroxyvitamin D3) in the liver and then to 1,25-dihydroxycholecalciferol (calcitriol) in the kidneys (Figure 1).2,15 The major circulating form, 25-hydroxycholecalciferol, is typically what is measured in laboratory tests, but conversion to 1,25-dihydroxycholecalciferol is required for activation. This conversion is stimulated by endogenous parathyroid hormone (PTH) in response to low calcium concentrations. Therefore, levels of 1,25-dihydroxycholecalciferol are not a good measure of vitamin D stores. Ergocalciferol (vitamin D2), in addition to cholecalciferol, can be obtained exogenously through dietary sources and supplements. Ergocalciferol also must be activated in the body similar to cholecalciferol. Calcitriol, the active form of vitamin D available by prescription only, also may be administered exogenously.

Exposure to ultraviolet B light is the main endogenous source of vitamin D. Several factors may diminish this exposure or the ability to activate vitamin D and thus may increase the risk for vitamin D deficiency, including the season, latitude, age,
skin pigmentation, and sunscreen use. In the United States, exposure to sunlight typically is lower during winter than during other seasons and at northern latitudes compared with southern latitudes. Elderly people who are housebound or live in nursing homes often have limited exposure to sunlight, and the ability to activate vitamin D decreases with advanced age. Vitamin D activation is lower in people with dark skin than in people with fair skin. The use of sunscreen to protect against skin cancer blocks ultraviolet light. Patients with intestinal malabsorption (e.g., inflammatory bowel disease) and those taking certain medications (e.g., phenytoin) are also at risk for vitamin D deficiency.

Diet is a minor source of vitamin D. Fatty fish (e.g., salmon and canned tuna) are the only foods naturally high in vitamin D, and only selected foods (e.g., cereals, milk) are fortified with vitamin D.

Vitamin D supplements are available that contain vitamin D alone or in combination with calcium. Vitamin D also is included in multivitamin products.

The 25-hydroxycholecalciferol level needed for optimal bone health is at least 30 ng/mL, but it should not exceed 100 ng/mL. A patient is considered deficient if the level is below 20 ng/mL. Many elderly and more than half of postmenopausal women receiving medications to treat or prevent osteoporosis in North America have vitamin D deficiency.

Inadequate levels of vitamin D often result in decreased GI calcium absorption and stimulation of PTH secretion, which causes compensatory bone resorption in an attempt to normalize serum calcium concentrations. Reduced bone mineralization and increases in bone turnover and loss associated with vitamin D deficiency increase the risk for fractures. Vitamin D receptors are present in skeletal muscle tissue, and vitamin D deficiency can impair muscle and neurological function, which increases the risk for falls and fractures, especially in the elderly. Impairment in the regulation of blood pressure, insulin production, and immune function, resulting in increased risk for cardiovascular disease, diabetes mellitus, autoimmune diseases, infections, and selected cancers (e.g., breast, colon), has also been suggested as a possible consequence of low vitamin D levels.

To prevent vitamin D deficiency, the NOF recommends a daily vitamin D intake of 400–800 units for adults less than 50 years of age and 800–1000 units for adults 50 years of age or older. Most postmenopausal women fall into the latter age group and require 800–1000 units/day. The two forms of vitamin D, cholecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂), appear to be equally effective; however, data are conflicting. Currently, a maximum daily vitamin D intake of 2000 units is recommended because of concern about increased risk for hypercalcemia. Many experts believe that a much higher daily intake (e.g., up to 4000 units) may be safe and required to prevent vitamin D deficiency in certain patient populations. An update of the dietary reference intakes for vitamin D by the Food and Nutrition Board is expected in mid 2010. Large 50,000-unit doses of vitamin D may be given orally once monthly instead of daily therapy to prevent vitamin D deficiency, especially if patient nonadherence is an issue. Ergocalciferol and cholecalciferol are available in a 50,000-unit strength by prescription and without a prescription, respectively.

The daily intake of vitamin D recommended by the NOF prevents vitamin D deficiency, but it is inadequate for treating vitamin D deficiency (i.e., 25-hydroxycholecalciferol <20 ng/mL). Large vitamin D doses are required on a short-term basis to raise levels above 30 ng/mL before switching to maintenance therapy. Guidelines for treating vitamin D deficiency are not available, so a variety of treatment regimens are used to achieve the target level, depending on the measured vitamin D level and patient characteristics (e.g., the presence of obesity or certain diseases). Prescription ergocalciferol 50,000 units orally once or twice weekly for approximately 8–12 weeks is a regimen commonly used until the vitamin D level rises above 30 ng/mL.

Normal bone remodeling

Bone is continuously remodeled through the coordinated activity of bone-resorbing osteoclasts and bone-forming osteoblasts. Osteoblast precursor cells produce receptor for activator of nuclear factor κB ligand (RANKL) in response to stimulation by various cytokines and growth factors, including 1,25-dihydroxyvitamin D (the active form of vitamin D), prostaglandin E₂, PTH, tumor necrosis factor α, and interleukins 1, 6, and 11. Binding of RANKL to its receptor, receptor for activator of nuclear factor κB (RANK), on osteoclasts and their precursors results in osteoclast differentiation, maturation, and activation. Mature osteoclasts bind to bone surfaces and secrete cathepsin K, which degrades the protein matrix in bone, and vacuolar hydrogen-adenosine triphosphatase, which produces acid that demineralizes hydroxyapatite, the major crystalline salt in bone matrix. These substances result in the formation of a cavity in the bone surface over the course of approximately three weeks. This process is terminated by the release of growth factors (e.g., platelet-derived growth factor, insulin-like growth factor I, transforming growth factor β) from bone during resorption. These growth factors stimulate the differentiation, maturation, and activation of osteoblasts, which produce osteoprotegerin (OPG), a soluble decoy protein that binds to RANKL. Binding of RANKL by
OPG prevents it from binding to its receptor RANK, which reduces the differentiation, maturation, and activation of new osteoclasts. Mature osteoclasts either undergo apoptosis (programmed death) or move to a new remodeling site. These effects turn off the bone resorption process. Mature osteoclasts then fill the bone cavity in a two-step process involving protein matrix deposition and mineralization with calcium, phosphate, and magnesium that takes approximately three months.

Pharmacologic therapies

A variety of medications are available for the management of postmenopausal osteoporosis (Table 2). Most of these agents are antiresorptive agents (i.e., inhibitors of bone resorption) that act directly or indirectly on osteoclasts to reduce their activity, number, or life span.

Bisphosphonates are structurally similar to pyrophosphate, a naturally occurring substance in the body. The drugs have a high affinity for and bind to exposed hydroxyapatite at sites of active bone resorption, where the drug is taken up by osteoclasts. The nitrogen-containing bisphosphonates block the enzyme farnesyl pyrophosphate synthase in the hydroxymethylglutaryl coenzyme A reductase pathway (also known as the mevalonate pathway) of osteoclasts. The blockage of this enzyme prevents adequate protein prenylation, reducing the activity of osteoclasts and ultimately leading to their death (apoptosis).39,50

The reduction in ovarian estrogen production results in increased bone resorption, partially through increases in the secretion of RANKL and decreases in the secretion of OPG.51 Estrogen replacement therapy decreases bone resorption by reversing these effects (i.e., increasing OPG and decreasing RANKL production).

Raloxifene is an estrogen agonist–antagonist (also referred to as a selective estrogen receptor modulator) with antagonist activity in breast tissue that protects against breast cancer and agonist activity in bone.52 This drug increases OPG production, thereby decreasing osteoclast differentiation, maturation, and activation.

Calcitonin is a natural polypeptide hormone produced by the parafollicular cells in humans. Salmon calcitonin is a synthetic form of this hormone with similar physiologic effects. These effects on bone are not completely understood, but they appear to involve direct inhibition of osteoclast function.53

Denosumab is a fully human monoclonal immunoglobulin G2 antibody against RANKL. It binds to RANKL in a manner similar to that of OPG, thereby preventing RANKL from binding to its receptor RANK, which reduces the differentiation, maturation, and activation of osteoclasts.34

Teriparatide is a recombinant product that contains the 34 amino acids of the biologically active region of human PTH.28 It is an anabolic agent that differs from antiresorptive agents because it primarily promotes bone formation by increasing osteoblast life span and function. The mechanism by which it exerts these effects is not completely clear.35

Selection considerations

In selecting from among the available medications for prevention and treatment of postmenopausal osteoporosis, efficacy, safety, route of administration, dosing frequency, and cost should be taken into consideration. Convenience, patient preference, potential for nonadherence, and need for extensive patient education about administration and storage also are considerations.

Efficacy. Efficacy comparisons ideally should be based on head-to-head comparative clinical trials of sufficient duration in which fractures (not bone mineral density [BMD]) are used as endpoints. No such trials exist; therefore, and data from pivotal clinical trials used to obtain Food and Drug Administration (FDA) approval are frequently used in therapeutic decision making.

Reductions in the risk for new vertebral fractures have been demonstrated with teriparatide and all of the currently available antiresorptive agents in pivotal placebo-controlled trials.27,36-42 The reduction in risk for new vertebral fractures ranged from 30% with raloxifene 60 mg daily (95% confidence interval [CI], 0.5–0.8) to 70% with zoledronic acid 5 mg every year (p < 0.001).39,40 Significant reductions in the risk for hip fractures after three years were demonstrated with some agents: 30% for risedronate 5 mg daily (p = 0.02), 40% for denosumab 60 mg every six months (p = 0.04), 41% for zoledronic acid 5 mg every year (p = 0.002), and 51% for alendronate 10 mg daily (95% CI, 0.23–0.99).27,36,39,41 Significant reductions in hip fracture were not demonstrated with the other agents, at least in part because the frequency of hip fracture without treatment is low and it is difficult to demonstrate differences with treatment. The teriparatide pivotal study was stopped early because of safety concerns raised in animal trials, before a difference in hip fractures was observed.42

Administration. Bisphosphonates are administered by the oral or intravenous (i.v.) route. Ibandronate injections are given over 15–30 seconds, and zoledronic acid is given as a 100-mL infusion over 15–30 seconds, and zoledronic acid 5 mg every year (95% CI, 0.5–0.8) to 70% with zoledronic acid 5 mg every year (p < 0.001).39,40 Significant reductions in the risk for new vertebral fractures have been demonstrated with teriparatide and all of the currently available antiresorptive agents in pivotal placebo-controlled trials.27,36-42 The reduction in risk for new vertebral fractures ranged from 30% with raloxifene 60 mg daily (95% confidence interval [CI], 0.5–0.8) to 70% with zoledronic acid 5 mg every year (p < 0.001).39,40 Significant reductions in the risk for hip fractures after three years were demonstrated with some agents: 30% for risedronate 5 mg daily (p = 0.02), 40% for denosumab 60 mg every six months (p = 0.04), 41% for zoledronic acid 5 mg every year (p = 0.002), and 51% for alendronate 10 mg daily (95% CI, 0.23–0.99).27,36,39,41 Significant reductions in hip fracture were not demonstrated with the other agents, at least in part because the frequency of hip fracture without treatment is low and it is difficult to demonstrate differences with treatment. The teriparatide pivotal study was stopped early because of safety concerns raised in animal trials, before a difference in hip fractures was observed.42

Am J Health-Syst Pharm—Vol 67 Apr 1, 2010 Suppl 3  S13

SYMPOSIUM Managing osteoporosis
Table 2.
Drug Therapies for Prevention or Treatment of Osteoporosis in Postmenopausal Women

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>FDA-Approved Doseb</th>
<th>Monthly Cost ($)c</th>
<th>Common Adverse Effects</th>
<th>Major Precautions and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bisphosphonates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>Prevention: 5 mg daily or 35 mg weekly</td>
<td>Generic: 9d</td>
<td>Abdominal pain, nausea, dyspepsia</td>
<td>Not recommended if CrCl &lt; 35 mL/min Contraindicated in hypocalcemia</td>
</tr>
<tr>
<td></td>
<td>Treatment: 10 mg daily or 70 mg weekly</td>
<td>Branded: 96e</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Prevention: 2.5 mg daily or 150 mg monthly Treatment: 2.5 mg daily, 150 mg monthly, or 3 mg i.v. every three months</td>
<td>Oral: 110 Injection: 115 (465 per injection)f</td>
<td>Oral: Abdominal pain, nausea, dyspepsia Injection: Acute-phase reaction usually resolving within 24–48 hours</td>
<td>Not recommended if CrCl &lt; 30 mL/min Contraindicated in hypocalcemia</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Prevention: 5 mg daily or 35 mg weekly Treatment: 5 mg daily, 35 mg weekly, 75 mg on two consecutive days/month, or 150 mg monthly</td>
<td>110</td>
<td>Abdominal pain, nausea, dyspepsia</td>
<td>Not recommended if CrCl &lt; 30 mL/min Contraindicated in hypocalcemia</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Prevention: 5 mg i.v. once every two years Treatment: 5 mg i.v. once every year</td>
<td>Prevention: 47 (1137 per injection)g Treatment: 95 (1137 per injection)g</td>
<td>Acute-phase reaction usually resolving within three days</td>
<td>Do not use if CrCl &lt; 35 mL/min Contraindicated in hypocalcemia</td>
</tr>
<tr>
<td><strong>Other Antiresorptive Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Prevention and treatment: 60 mg daily</td>
<td>123</td>
<td>Hot flashes, leg cramps, peripheral edema</td>
<td>Use with caution in patients at risk for stroke Contraindicated in patients with history of VTE</td>
</tr>
<tr>
<td>Calcitonin salmon</td>
<td>Treatment: 200 units daily intranasally, alternating nostrils dailyh</td>
<td>Generic: 75 Branded: 123</td>
<td>Nasal irritation and dryness, epistaxis</td>
<td>None</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Treatment: 60 mg s.c. every six monthsi</td>
<td>N/A</td>
<td>Cellulitis, eczema, flatulence</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Anabolic Agent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Treatment: 20 mcg s.c. daily</td>
<td>870</td>
<td>Transient hypercalcemia,1 arthralgia, dizziness</td>
<td>Do not use in patients at risk for osteosarcoma</td>
</tr>
</tbody>
</table>

1CrCl = creatinine clearance; i.v. = intravenously; VTE = venous thromboembolism; FDA = Food and Drug Administration; s.c. = subcutaneously; N/A = not available.
2All therapies are administered orally except where otherwise specified.
3Price from www.drugstore.com (October 2009), except where noted.
4Price from Walmart and Target (October 2009).
5Alendronate is the only bisphosphonate available as an oral liquid (in single-dose bottles containing 70 mg/75 mL) and in combination with vitamin D3 (tablets containing alendronate 70 mg plus cholecalciferol 2800 units or 5600 units).
6Medicare Part B pays 80%.
7Acute-phase reactions are characterized by influenza-like illness, fever, headache, myalgia, and arthralgia.
8Calcitonin salmon is approved by FDA for the treatment of postmenopausal osteoporosis only in women who are more than 5 years beyond menopause.
9FDA decision regarding approval anticipated in July 2010.
10Patients should be advised to report symptoms of hypercalcemia (e.g., nausea, vomiting, constipation, lethargy, muscle weakness) during teriparatide therapy.
could increase the risk for adverse effects and reduce GI absorption and efficacy. These requirements and a patient’s ability to meet them may influence the selection of drug therapy for prevention or treatment of osteoporosis.

Dosing frequency may be an important consideration in choosing among drug therapies for osteoporosis prevention and treatment. One-year rates of adherence to oral osteoporosis therapies generally are poor (i.e., many patients discontinue their medication within one year). These rates decrease progressively as the dosing frequency increases, from 50% to 60% with monthly therapy to 40% to 50% with weekly therapy and 20% to 40% with daily therapy. Poor adherence is associated with reduced efficacy and an increased risk for fractures (i.e., these outcomes may be an indirect effect of frequent dosing).

The intranasal route of administration of calcitonin salmon and the subcutaneous (s.c.) route of administration of denosumab and teriparatide may be an advantage or a disadvantage, depending on patient preference. The need for daily s.c. injections and unique storage requirements are potential disadvantages of teriparatide. The drug is provided in a prefilled pen or delivery device that must be stored under refrigeration (36 °F to 46 °F) and protected from freezing at all times. The pen or delivery device should be discarded 28 days after first use or if freezing occurs. These storage requirements may pose challenges for patients, especially during airline travel.

Cost. The monthly costs of most oral bisphosphonates, raloxifene, and calcitonin salmon are comparable, but alendronate and calcitonin salmon are now available in generic forms at lower costs than the brand name products (Table 2). Even though injectable products are administered less frequently, the monthly cost of injectable ibandronate and zoledronic acid is higher than the cost of oral bisphosphonates because of fees for administration by a health care provider. Medicare Part B covers 80% of the cost of injectable ibandronate and zoledronic acid. The cost of denosumab, which also would need to be administered by a health care provider, is unknown. Teriparatide is particularly costly, although patient assistance programs are available.

Safety. Adverse effects, precautions, and contraindications may limit the use of certain medications for the prevention or treatment of osteoporosis (Table 2). Abdominal pain, nausea, and dyspepsia are common from oral bisphosphonates. Dysphagia and esophageal irritation and ulceration are uncommon when oral administration instructions (i.e., taking with a full glass of plain water and avoiding lying down) are followed. Injectable bisphosphonates do not cause abdominal pain, nausea, or dyspepsia, but they can cause acute-phase reactions (e.g., influenza-like illness, fever, headache, myalgia, arthralgia) that last up to several days. The occurrence of these reactions often diminishes after subsequent doses.

Bone, joint, and muscle pain and osteonecrosis of the jaw occur rarely in patients receiving oral or injectable bisphosphonates. Osteonecrosis of the jaw is a rare adverse effect of bisphosphonates seen primarily in patients with cancer undergoing dental procedures and receiving high-dose i.v. bisphosphonate therapy. The estimated frequency of jaw osteonecrosis in patients receiving bisphosphonates for osteoporosis is less than one case per 100,000 person-years of exposure. Nevertheless, patients with or at risk for postmenopausal osteoporosis should complete extensive dental work before initiating oral or i.v. bisphosphonate therapy, undergo routine dental examinations and use good oral hygiene during such therapy, and consider stopping the drug if jaw osteonecrosis is suspected or confirmed.

Stopping bisphosphonate therapy before an invasive dental procedure will not be beneficial because of the long half-life of the drugs.

Oral and injectable bisphosphonates are not recommended for patients with severe renal impairment. The drugs are contraindicated in patients with hypocalcemia.

Common adverse effects from raloxifene include hot flashes, leg cramps, and peripheral edema. Hot flashes are most common during the first six months of treatment.

Raloxifene is contraindicated in patients with history of venous thromboembolism (deep vein thrombosis, pulmonary embolism, or both) because it increases the risk of these effects, especially during the first four months of treatment. Raloxifene increased the risk for death from stroke in a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk for coronary events. Therefore, the drug should be used with caution in patients with a history of stroke or transient ischemic attack, atrial fibrillation, hypertension, or cigarette smoking as these factors increase the risk of an intial or subsequent stroke.

Calcitonin salmon nasal spray causes minimal adverse effects, primarily nasal irritation and dryness and epistaxis (nosebleeds). The drug usually is well tolerated.

Denosumab has been associated with a small but statistically significant increased risk for cellulitis (0.3% vs. 0.1%, p = 0.002), eczema (3% vs. 1.7%, p < 0.001), and flatulence (2.2% vs. 1.4%, p < 0.008) in postmenopausal women with osteoporosis. In postmenopausal women with osteopenia, an increased risk for serious infections was also noted (4.9% vs. 0.6%, p = 0.020). It is likely that if approved, package labeling will include precautions regarding infection risk. In addition,
the FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for denosumab and must include a medication guide, a communication plan, and a timetable for submission of assessments of the REMS. The drug should not be used in patients at increased risk for osteosarcoma (e.g., patients with a history of external beam or implant radiation therapy involving the skeleton).

**Role in therapy**

Specific guidelines for which of the available osteoporosis medications are considered first-, second-, and third-line therapies are not available, so expert opinion is relied on for therapeutic decision making. Oral bisphosphonates generally are preferred (i.e., considered first-line therapy) because of their efficacy, relative safety, convenience, and the variety of possible dosing frequencies, some of which may promote adherence. The infrequent administration of injectable bisphosphonates may promote adherence, and the efficacy of these products (particularly zoledronic acid) is well documented. However, because of the higher cost, most health insurance companies do not cover injectable bisphosphonates unless a patient has a documented problem with nonadherence to or intolerance of oral bisphosphonates.

Raloxifene may be a good choice for women who cannot take or tolerate bisphosphonates and are at high risk for fractures and breast cancer, although the potential for hot flashes and risk for stroke and venous thromboembolism should be taken into consideration. Teriparatide usually is reserved for the treatment of women with established postmenopausal osteoporosis and a very low BMD (i.e., T-score ≤ −3.5); multiple fractures, a high risk for fractures, or contraindications to or an inability to tolerate bisphosphonates or raloxifene. Although calcitonin salmon is well tolerated, it can be considered a last-line option for patients who are unable to use other therapies because of its limited efficacy and the need for daily doses, which can reduce adherence.

In August 2009, the FDA Advisory Committee for Reproductive Health Drugs voted to approve denosumab for the treatment of postmenopausal osteoporosis. However, in October 2009, the FDA issued a Complete Response Letter to request additional information in order to complete the review of application for product approval. Additional pre-marketing clinical trials were not deemed necessary. Based on its review of the Complete Response Submission, the FDA indicated that it will make a decision regarding the approval of denosumab for the treatment of postmenopausal osteoporosis in July 2010. The infrequent dosing (once every six months) and the positive efficacy results from clinical studies make denosumab a potentially promising new drug.

Combinations of two antiresorptive agents or an antiresorptive agent and an anabolic agent have been tried in patients with osteoporosis, with mixed results. The effect of combination therapy on fracture risk has not been studied. Because combination therapy has the potential to increase adverse effects, cost, and nonadherence, it cannot be recommended at this time.

**Pharmacist’s role**

Health-system pharmacists play an important role in managing postmenopausal osteoporosis and preventing falls and fractures by counseling postmenopausal women about bone-healthy lifestyle modifications (regular weight-bearing and resistance exercise, smoking cessation, limiting alcohol and caffeine intake, and achieving adequate intakes of calcium and vitamin D through diet and supplements) and ways to reduce their fall risk. How to attain adequate intakes of calcium and vitamin D through diet and the use of supplements if needed, the proper use of drug therapies to prevent and treat osteoporosis, and ways to avoid or minimize adverse effects should be part of patient counseling. The use of some osteoporosis medications requires extensive patient education (e.g., requirements for the safe and effective administration of oral bisphosphonates and the storage of teriparatide), and pharmacists are the ideal health care professionals to provide this education.

Because patients with osteopenia and osteoporosis have no symptoms or other observable adverse health consequences unless they experience a fracture, pharmacists must continually reinforce the importance of adhering to drug therapies and other interventions for preventing and treating postmenopausal osteoporosis. Dual-energy X-ray absorptiometry (DXA) scans are not performed often enough to provide the feedback that many patients need about the impact of medication adherence in improving or preserving BMD or the consequences of nonadherence. Evidence of a positive impact often is needed to reinforce adherence.

Health-system pharmacists can improve the health of postmenopausal women with or at risk for osteoporosis by making recommendations for drug therapy to prevent or treat the disease. These recommendations should take into consideration patient characteristics and preferences and drug efficacy, safety, route
SYMPHOSUM Managing osteoporosis

of administration, dosing frequency, convenience, cost, and potential for nonadherence. Reviewing the patient medication profile for medications that increase the risk for falling and for potential drug interactions (especially involving calcium) can contribute to improved outcomes.

Application to patient cases

The following discussion of two cases illustrates the patient assessment and therapeutic decision-making processes used by pharmacists for postmenopausal women.

Patient AB. AB is a 68-year-old Caucasian woman who presents to the clinic for follow-up of a DXA scan three weeks ago. Her past medical history includes deep vein thrombosis (DVT) 10 years ago after a hysterectomy. She also has hypertension, which was diagnosed five years ago and for which she takes hydrochlorothiazide 25 mg orally once daily. AB also takes a calcium carbonate product that contains 600 mg of elemental calcium orally once daily with a meal. Her family history is notable for breast cancer once her mother. AB smokes cigarettes (one pack per day for 40 years), but she does not consume alcohol and/or abuse intravenous drugs. Her relevant vital signs, DXA T-scores, and laboratory test results are as follows:

- Systolic/diastolic blood pressure: 134/74 mm Hg
- Weight: 125 lb
- Height: 5'3"
- DXA T-score: –2.6 right femur, –2.4 left femur
- 25-hydroxyvitamin D: 45 ng/mL

BMD testing is warranted for AB because of her age (testing is recommended by the NOF for women ≥ 65 years). The right femur T-score confirms a diagnosis of osteoporosis for AB because it is less than the –2.5 cutoff value used in the World Health Organization (WHO) diagnostic criteria. According to the NOF, treatment is indicated for AB because her T-score is less than –2.5 and it is not necessary to perform a calculation using the FRAX fracture risk assessment tool because AB is clearly at high risk on the basis of her T-score alone, although her advanced age, cigarette smoking, and small frame (she is petite at a height of 5'3" with a weight of only 125 lb) also contribute to her increased risk.

An oral bisphosphonate (daily or weekly alendronate; daily or monthly ibandronate; or daily, weekly, or monthly risedronate) is the treatment of first choice for AB because of its efficacy and relative safety. AB prefers an oral agent because out-of-pocket cost is a concern, and her health insurance does not cover intravenous bisphosphonates. Weekly generic alendronate is the least costly oral bisphosphonate. AB should be counseled about the proper administration of oral bisphosphonates to minimize risk for adverse effects and to maximize efficacy. If adherence to a weekly oral bisphosphonate becomes a problem, AB could receive a brand-name oral therapy on a monthly basis instead.

Raloxifene is contraindicated for AB because her history of DVT increases her risk of venous thromboembolism during raloxifene therapy. Teriparatide is not the best choice for AB because it is reserved for the treatment of women with established postmenopausal osteoporosis and a very low BMD (i.e., T-score ≤ –3.5), multiple fractures, a high risk of fractures, or contraindications to or an inability to tolerate bisphosphonates or raloxifene. Calcitonin salmon is probably the last resort for AB because of its limited efficacy.

AB’s daily intake of elemental calcium and vitamin D from foods and supplements should be at least 1200 mg and 800–1000 units, respectively, because she is more than 50 years old. AB takes a calcium supplement that provides 600 mg of elemental calcium per day. Since the average daily dietary calcium intake in women 60 years of age or older is 660 mg, AB’s daily intake of calcium may be adequate. If she is unable to consistently consume at least 600 mg of dietary calcium on a daily basis, an increase in her supplemental intake will be needed. AB does not take a vitamin D supplement. Although her vitamin D level is within the desired range (>30 ng/mL), a daily intake of 800–1000 units will be needed to keep her in this range over the long term. As dietary intake of vitamin D is minimal, AB should be advised to start taking a daily supplement that contains 800–1000 units of vitamin D. AB could consider using a combination product that contains calcium and vitamin D or use separate supplements. It is important to remember that most multivitamin products contain at least 400 units of vitamin D.

AB also should be educated on the harmful effects of cigarette smoking and the beneficial effects of quitting, as well as given assistance regarding ways to quit. Participation in weight-bearing and resistance exercise to promote bone health and achieve other health benefits will also be important.

Patient CD. CD is a 74-year-old black woman who presents to the clinic for follow up of a DXA scan two months ago. Her past medical history includes osteoarthritis, gastroesophageal reflux disease (GERD), and a wrist fracture after falling on the ice one year ago. CD takes acetaminophen 500 mg orally twice daily for the osteoarthritis and lansoprazole 30 mg orally once daily for GERD. Her father suffered a hip fracture, but her family medical history is otherwise unremarkable. CD does not smoke cigarettes, consume alcohol, or abuse intravenous drugs. Her relevant vital signs, DXA T-scores, and laboratory test results are as follows:

- Weight: 115 lb
- Height: 5’2”
- DXA T-score: –1.8 right femur, –1.9 left femur
- 25-hydroxyvitamin D: 15 ng/mL
BMD testing was warranted for CD because of her fracture and age (testing is recommended by the NOF for persons with a prior fracture and women ≥65 years).1 Her T-scores fall in the range for osteopenia (−1.0 to −2.5) in the WHO diagnostic criteria.1,49 Although CD has had a fracture, the decision to treat her is not straightforward because the fracture involved her wrist, not her spine or hip (a fracture of the vertebrae or hip is sufficient to justify initiating treatment regardless of T-scores, according to the NOF).2 It is unclear whether to initiate treatment for CD on the basis of her T-scores alone because she does not have osteoporosis. Treatment decisions for patients such as CD with osteopenia hinge on the 10-year probability of fractures calculated with the online FRAX fracture risk assessment tool available from the WHO (http://www.shef.ac.uk/FRAX/).55 Using the FRAX tool for black Americans, CD has a 10-year probability of a major osteoporotic fracture of 13% and a 10-year probability of a hip fracture of 6.4%. This calculation takes into account CD’s advanced age, female sex, low weight, petite height, prior wrist fracture, father’s hip fracture, and low femur T-score. Treatment is indicated for CD because she has osteopenia and her 10-year probability of a hip fracture exceeds 3%, which is the threshold above which treatment is indicated in patients with osteopenia, according to the NOE.1

An oral bisphosphonate is the drug of first choice for CD. The choice among oral products might hinge on dosing frequency, cost, convenience, and CD’s preference. An injectable bisphosphonate is an alternative for CD, especially if her GERD worsens during oral therapy. Oral bisphosphonates can cause dyspepsia and esophageal irritation. CD should be advised on proper administration to avoid or minimize these problems.

Raloxifene is an alternative for CD if she cannot tolerate bisphosphonates.20 Teriparatide is not the best choice for CD because it is reserved for the treatment of women with established postmenopausal osteoporosis and a very low BMD (i.e., T-score ≤ −3.5), multiple fractures, a high risk of fractures, or contraindications to or an inability to tolerate bisphosphonates or raloxifene.2,52 Calcitonin salmon is also a last-line option for CD because of less robust efficacy data.26 CD’s 25-hydroxyvitamin D level (15 ng/mL) is low (the desired level is >30 ng/mL), reflecting vitamin D deficiency. One option for repletion is prescription ergocalciferol 50,000 units orally weekly for eight weeks.14,15 Once CD’s vitamin D level increases to the target range, she can switch to maintenance therapy with 800–1000 units/day as ergocalciferol or cholecalciferol. CD also should consume at least 1200 mg/day of elemental calcium. Her dietary calcium intake probably is inadequate if it is typical of that of most women her age.6 She should take a calcium supplement, and calcium citrate is preferred over calcium carbonate for elderly patients like CD who take proton pump inhibitors.2 A combination product containing both calcium citrate and vitamin D should promote adherence.

Fall prevention strategies are an important component of a bone-healthy lifestyle for CD because of her wrist fracture from falling on ice. None of her medications increases her risk for falling, and she does not drink alcohol. However, CD should have her vision checked and her home assessed for safety hazards that could increase the risk for falls (e.g., poor lighting, loose throw rugs, tripping hazards).

Conclusion The management of osteoporosis in postmenopausal women involves a bone-healthy lifestyle, adequate calcium and vitamin D intake, and various drug therapies. Health-system pharmacists can improve bone health in postmenopausal women by making recommendations for these management strategies and counseling patients.

References
**SYMPOSIUM**

**Managing osteoporosis**


Managing cancer treatment-induced bone loss and osteoporosis in patients with breast or prostate cancer

LAURA BOEHNKE MICHAUD

Purpose. To discuss trends in breast and prostate cancer prevalence and survival; risk factors for bone loss, osteoporosis, and fractures and the approach to risk assessment in patients with these malignancies; established and investigational drug therapies for managing cancer treatment-induced bone loss and osteoporosis; and the role of health-system pharmacists in promoting bone health in patients with breast or prostate cancer.

Summary. Breast cancer and prostate cancer are common, deadly diseases, but many survivors are alive today because of improvements in early detection and treatment over the past 10–15 years. Cancer chemotherapy, corticosteroids, hormone-ablation therapy, and other common risk factors place patients with breast or prostate cancer at high risk for bone loss, osteoporosis, and fractures. Most patients with breast or prostate cancer should undergo assessment of risk for bone loss and osteoporosis that involves a bone-related history and physical examination, dual-energy X-ray absorptiometry scanning, and the FRAX fracture risk assessment tool from the World Health Organization. A recent National Comprehensive Cancer Network task force report on bone health in cancer care provides recommendations for considering the use of pharmacologic therapy on the basis of the results of this assessment. Bisphosphonates are useful for slowing or preventing bone loss associated with hormone-ablation therapy in women with breast cancer and men with prostate cancer, although fracture data are limited in women and not available in men. The usefulness of other therapies (selective estrogen receptor modulators, teriparatide, calcitonin salmon, and estrogens) is limited by adverse effects, a lack of experience with the drugs in these patient populations, or both. Various drug therapies are in development for managing cancer treatment-induced bone loss and osteoporosis. The agent closest to approval by the Food and Drug Administration, denosumab, has been shown to improve bone mineral density in women and men receiving hormone-ablation therapy for breast or prostate cancer, but additional data are needed to dispel safety concerns that could limit the use of this drug in these patient populations. Health-system pharmacists play an important role in screening patients with a history of breast or prostate cancer for bone loss or osteoporosis, making drug therapy recommendations to address the problem, and counseling patients on modifiable risk factors for osteoporosis and proper use of drug therapies to improve bone health.

Conclusion. Health-system pharmacists can improve the detection and management of cancer treatment-induced bone loss and osteoporosis in patients receiving systemic therapy for breast or prostate cancer.

Index terms: Antibodies; Antineoplastic agents; Bisphosphonates; Bone density; Breast neoplasms; Denosumab; Diagnosis; Fractures; Mortality; Osteoporosis; Patient education; Pharmacists, hospital; Prostate neoplasms; Sex steroids, corticosteroids; Toxicity


Breast cancer and prostate cancer are the most commonly diagnosed malignancies in women and men, respectively, in the United States. In 2009, breast cancer accounted for an estimated 27% of new cancer cases in women, and prostate cancer accounted for 25% of new cancer cases in men. Nearly 200,000 cases of each type of cancer are diagnosed in the United States annually.

Breast and prostate cancer are the second most common causes of cancer death (after cancer of the lung...
and bronchus) in American women and men, respectively. In 2009, breast cancer was responsible for 15% of cancer deaths in American women, and prostate cancer accounted for 9% of cancer deaths in American men.1

The age-adjusted death rate from breast cancer in women began to decrease in 1990; it decreased by 27% between 1990 and 2005 (the most recent year for which data are available).2 Similarly, the death rate from prostate cancer began to decrease in the mid-1990s and decreased steadily through 2005.2 The decreases in breast and prostate cancer mortality have been attributed to improvements in early detection and treatment.1,3 Substantial numbers of survivors of these malignancies are alive today. For example, approximately 2.5 million women with a history of breast cancer were alive in January 2006.3

**Risk for osteoporosis and fractures**

Bone health is a concern for many patients with breast or prostate cancer because many of their treatments cause bone loss (cancer treatment-induced bone loss). The bones are a common site of metastases with breast and prostate cancers, but bone metastases and their treatment are beyond the scope of this article.

Factors that increase the risk for osteoporosis and fractures are listed in Table 1. Patients with breast or prostate cancer may have any of these risk factors, but certain risk factors are more common than others in these patient populations.

**Breast cancer patients.** Premature ovarian failure (i.e., early menopause) is a risk factor for osteoporosis and fractures in women with breast cancer because of the loss of estrogen. Premature ovarian failure may occur as an unintended result of the cancer chemotherapy used to eradicate residual cancer cells in women with early-stage breast cancer. Chemotherapy also may have a direct effect on bone.5 Premature ovarian failure also may be produced intentionally through oophorectomy (surgical removal of the ovaries) or drug therapy using luteinizing hormone releasing hormone (LHRH) agonists (e.g., goserelin, leuprolide, triptorelin) in premenopausal women with breast cancer. In postmenopausal women with breast cancer, the use of other endocrine therapies, most notably aromatase inhibitors (e.g., anastrozole, letrozole, exemestane), causes bone loss and increases the risk for osteoporosis and fractures. These drugs inhibit the synthesis of estrogen and reduce estrogen levels so that they are barely detectable and much lower than levels associated with natural menopause.

Some antitumor therapies used in women with breast cancer may prevent bone loss, which may reduce the risk for osteoporosis and fractures in postmenopausal women. Two such drugs, the selective estrogen receptor modulators (SERMs, also known as estrogen agonist–antagonists) tamoxifen and toremifene, are approved by the Food and Drug Administration (FDA) for the treatment of breast cancer.6,7 A third SERM, raloxifene, is used to reduce the risk of invasive breast cancer in postmenopausal women at high risk for the malignancy or with osteoporosis.8 Raloxifene is not used to treat breast cancer. These agents may have different effects on bone in premenopausal women in whom circulating estrogen levels are high.

Corticosteroids also can cause bone loss. These agents typically are not administered on a long-term basis as part of modern breast cancer treatment regimens, although they are used intermittently for supportive care (i.e., as antiemetic agents and to prevent allergic reactions) with chemotherapy. Bone loss from corticosteroids usually is the result of long-term use of these drugs, and most patients with breast cancer do not receive corticosteroids on a long-term basis.

Inadequate calcium intake, vitamin D deficiency, and inadequate exercise increase the risk for osteoporosis and fractures as well, and these risk factors are common in cancer patients. There is evidence that vitamin D deficiency is particularly common in women with breast cancer.9 Patients with cancer also may smoke cigarettes or consume excessive alcohol

<table>
<thead>
<tr>
<th>Table 1. Risk Factors for Osteoporosis and Fractures4</th>
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<tbody>
<tr>
<td>Advanced age (≥50 years old)</td>
</tr>
<tr>
<td>Lifestyle (e.g., low calcium intake, vitamin D insufficiency, inadequate exercise, cigarette smoking, high alcohol intake)</td>
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<tr>
<td>Genetics (e.g., parental history of hip fracture)</td>
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<tr>
<td>Hypogonadal states (e.g., premature ovarian failure)</td>
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<td>Endocrine disordersa</td>
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<td>Gastrointestinal disorders</td>
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<tr>
<td>Hematologic disorders</td>
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<tr>
<td>Rheumatic and autoimmune diseases</td>
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<td>Medicationsa</td>
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<tr>
<td>Cancer chemotherapy</td>
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<tr>
<td>Aromatase inhibitors</td>
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<tr>
<td>Luteinizing hormone releasing hormone (gonadotropin releasing hormone) agonists</td>
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<tr>
<td>Corticosteroids</td>
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*aA common risk factor in patients with breast or prostate cancer.*
Androgen-deprivation is the cornerstone of prostate cancer treatment. Androgen-deprivation therapy to reduce blood levels of testosterone as a result of cancer treatment. This endocrine disorder should be taken into consideration in evaluating the risk for osteoporosis and fractures in a woman with breast cancer.

Prostate cancer patients. Men with prostate cancer may have hypogonadism as an underlying condition or, more commonly, as a result of cancer treatment. Androgen-deprivation therapy to reduce blood levels of testosterone is the cornerstone of prostate cancer treatment. Androgen-deprivation therapy involves surgical testicular ablation through orchietomy (i.e., removal of the testes) or medical testicular ablation using an LHRH agonist. This hormone-ablation therapy may be used with or without a nonsteroidal antiandrogen, such as bicalutamide or flutamide. This approach to prostate cancer treatment is analogous to the hormone-ablation therapy used for breast cancer treatment; cancer cell growth is impaired by depriving the cells of hormonal stimulation. Unfortunately, hormone-ablation therapy promotes bone loss and increases the risk for osteoporosis and fractures in both men and women.

Androgen-deprivation therapy may be used as adjuvant therapy for locally advanced prostate cancer. It also may be used in patients with a prior diagnosis and rising prostate-specific antigen (PSA) levels, suggesting disease recurrence in the absence of overt evidence of metastasis. The median time between PSA level elevation and the detection of metastases is long (eight years). Early use of androgen-deprivation therapy when PSA elevation is detected may be preferable to later use. Therefore, androgen-deprivation therapy may be administered for long periods of time. However, the survival time of men with advanced prostate cancer is long even after metastases are detected (a median of five years after detection of metastases), and the benefit of early androgen-deprivation therapy instead of delayed therapy is unclear.

Corticosteroids are used for prostate cancer only if it is metastatic. The use of corticosteroids after androgen-deprivation therapy provides a two-pronged approach to treating the disease. Methylprednisolone is a common component of chemotherapy regimens for hormone-refractory prostate cancer (HRPC). Prednisone or dexamethasone may often be used instead in combination with docetaxel. Prednisone and mitoxantrone historically was another combination regimen for HRPC but is now used only as salvage therapy.

Many men with prostate cancer have a low bone mineral density (BMD) before cancer treatment begins because of the risk factors listed in Table 1. These risk factors and the use of chemotherapy, corticosteroids, and hormone-ablation therapy can have an additive effect to worsen bone loss and increase the risk for osteoporosis and fractures in men with prostate cancer.

Patient assessment

The National Osteoporosis Foundation (NOF) recommends BMD testing for the general population (i.e., regardless of the presence of malignancy) in women 65 years of age or older and men 70 years of age or older regardless of clinical risk factors. Younger postmenopausal women and men 50–69 years of age with risk factors also should be tested, according to NOF guidelines.

A task force of the National Comprehensive Cancer Network (NCCN) recently issued a report on bone health in cancer care. This task force report is not a clinical practice guideline, and outcomes related to its recommendations are not yet available. However, the process used in developing the task force report was similar to that used in the development of clinical practice guidelines. According to NCCN, all patients who begin cancer therapy that induces early menopause, reduces sex steroids or interferes with their action, or includes corticosteroids should undergo assessment of bone loss risk and subsequent risk of osteoporosis and fractures. Most patients with breast cancer or prostate cancer meet one or more of these criteria. The fracture risk should be assessed by obtaining a bone-related history and physical examination, performing dual-energy X-ray absorptiometry (DXA) scans, and using the FRAX fracture risk assessment tool available from the World Health Organization (http://www.shef.ac.uk/FRAX/). A stooped posture reflecting vertebral compression fractures may serve as an obvious clue that osteoporosis is present in women, but it is often a late sign of bone disease.

Patients with cancer and an elevated fracture risk should be evaluated every 24 months to monitor the impact of cancer treatment on bone mass. A 12-month follow-up DXA scan may be reasonable if the risk for bone loss changes substantially or major therapeutic intervention is undertaken (e.g., initiation of a bisphosphonate).

Bone management strategies

According to the NCCN task force report, pharmacologic therapy for low bone mass should be considered for patients with cancer and a T-score between –1.5 and –2.0 (i.e., in the range considered osteopenia). Pharmacologic therapy should be strongly considered...
for patients with cancer and either of the following:
- T-score <−2.0 or
- 10-year risk for major fracture >20% or 10-year risk for hip fracture >3% using the FRAX fracture risk assessment tool.14

Pharmacologic options include bisphosphonates, SERMs, teriparatide, calcitonin salmon, and estrogens.

**Breast cancer.** In women with breast cancer and premature ovarian failure, bone loss is significantly greater than that associated with natural menopause or aromatase inhibitor use.14 Bisphosphonates attenuate bone loss associated with ovarian failure.14 In patients without cancer, these drugs reduce fractures at vertebral, hip, and other non-vertebral sites.15

The effect on lumbar spine BMD of early and delayed treatment with the bisphosphonate zoledronic acid 4 mg intravenously (i.v.) every three months was compared with a control group in whom treatment was delayed until one year after chemotherapy in a study of premenopausal women with breast cancer who were initiating adjuvant chemotherapy.14 There was a 6.6% loss of BMD in the lumbar spine over the course of one year in the control group.

The effect of zoledronic acid 4 mg i.v. every six months for three years was evaluated in a randomized, open-label study of 404 premenopausal women with early breast cancer who were receiving endocrine therapy (the LHRH agonist goserelin plus either the SERM tamoxifen or the aromatase inhibitor anastrozole). Measurements of BMD at the lumbar spine and trochanter (a bony protuberance near the top of the femur) were stable over the three-year period in patients who received zoledronic acid with endocrine therapy. However, BMD decreased significantly at the lumbar spine by 11.3% (p < 0.0001) and trochanter by 7.3% (p < 0.0001) after three years of treatment with endocrine therapy alone (i.e., without zoledronic acid).17 Adding zoledronic acid to endocrine therapy significantly improved disease-free survival after 47.8 months from 90.8% to 94.0% (p = 0.01) and reduced the risk of disease progression by 36% (p = 0.01).18 The hazard ratio for risk of death in patients receiving zoledronic acid was 0.60, which was not significant (p = 0.11), probably because of the relatively short duration of the study (7–10 years usually is needed to detect survival differences in breast cancer chemotherapy clinical trials) and the small number of deaths (16 in zoledronic acid–treated patients and 26 in patients not treated with the drug). Fracture data are not yet available from studies of zoledronic acid in patients with breast cancer. Clearly, more data are needed before the incorporation of bisphosphonates can be considered standard in this patient population.

The benefits of bisphosphonates in women with breast cancer who receive aromatase inhibitors are less clear than the benefits of use of the drugs in women with premature ovarian suppression. In two studies of postmenopausal women with early breast cancer who were receiving the aromatase inhibitor anastrozole, favorable effects on BMD were demonstrated with the use of a bisphosphonate (risedronate in one study and ibandronate in the other study) over a 24-month period.19,20 In these two studies, patients with osteopenia were randomly assigned to receive the bisphosphonate or placebo, but patients with osteoporosis received the bisphosphonate on an open-label basis. Therefore, the study results should be interpreted with caution. Also, fracture data are not available from these studies.

Limited fracture data are available from two studies with similar methods that compared early and delayed zoledronic acid therapy in a total of 1667 postmenopausal women with early breast cancer who were receiving the aromatase inhibitor letrozole, although these studies were not designed to evaluate efficacy for reducing fractures.21 Women in the delayed groups received zoledronic acid only if their lumbar spine or total hip T-score fell below −2.0 or they experienced a nontraumatic fracture. After 12 months, the rate of fractures was 2.2% with early zoledronic acid and 2.1% with delayed zoledronic acid. Statistical analysis was not possible because of the small numbers of fractures.21 After 36 months, the rate of fractures was slightly higher in the delayed group (6.3%) than in the early group (5.7%), but the difference was not significant (p = 0.8638).22

Osteopenia prior to the initiation of aromatase inhibitors appears to be a risk factor for aromatase inhibitor–induced bone loss in women with breast cancer.23 The potential for development of osteoporosis in patients receiving aromatase inhibitors may be limited to those with low baseline BMD values.24 These observations suggest that women with breast cancer and osteopenia who require aromatase inhibitors should receive treatment to prevent bone loss, although the use of bisphosphonates to prevent bone loss in this patient population remains the subject of debate.25 At the University of Texas M. D. Anderson Cancer Center, women with breast cancer are screened for osteopenia with a baseline BMD measurement before the initiation of aromatase inhibitors.

Although breast cancer patients appear to benefit from bisphosphonate therapy, these agents are associated with some significant side effects. Oral bisphosphonates should be used with caution in patients with esophageal disorders because the drugs can cause local irritation of the upper gastrointestinal (GI)
mucosa. Bisphosphonates are not recommended for patients with severe renal impairment.

Osteonecrosis of the jaw is a rare adverse effect of bisphosphonates that is seen primarily in patients with cancer undergoing dental procedures and receiving i.v. bisphosphonates. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with a history of cancer, chemotherapy, radiotherapy, corticosteroids, or other risk factors. These patients should avoid invasive dental procedures if possible during bisphosphate treatment.

Tamoxifen is used for the treatment of breast cancer in all stages of the disease and to reduce the risk of breast cancer in women who are at high risk for the malignancy. The drug has beneficial effects on BMD in postmenopausal women with breast cancer, but its use for this purpose is controversial. Tamoxifen is not approved by FDA for the prevention or treatment of osteoporosis. The drug can cause life-threatening complications, particularly venous thromboembolism and endometrial cancer. Venous thromboembolism is a particular concern for patients with cancer because an increased risk for thrombosis is associated with malignancy as well. The concurrent use of tamoxifen with an aromatase inhibitor appears to lead to decreased antitumor efficacy of anastrozole and should be avoided.

The SERM raloxifene is approved by FDA to treat and prevent osteoporosis in postmenopausal women. Raloxifene reduces the risk of vertebral fractures, but it has no effect on the rate of hip or other nonvertebral fractures and indirectly appears to be less effective than the bisphosphonates. Adverse effects from raloxifene include an increased risk for thromboembolism. Although raloxifene generally is thought to be less likely than tamoxifen to cause endometrial cancer, endometrial effects have been reported from use of the drug. Because of the interaction between tamoxifen and the aromatase inhibitors, there is concern that a similar interaction between raloxifene and the aromatase inhibitors may occur. Therefore, the concurrent administration of the SERMs with aromatase inhibitors should be avoided.

The use of a bisphosphonate is preferred over the use of tamoxifen and other SERMs for improving or maintaining BMD in women with breast cancer and osteopenia or osteoporosis. Bisphosphonates have more potent antiresorptive effects than SERMs and appear to lead to better clinical outcomes.

Teriparatide (a recombinant product containing the biologically active fragment of human parathyroid hormone) is approved by the FDA for treatment of osteoporosis in men and women. However, teriparatide increased the frequency of osteosarcoma (a malignant bone tumor) in animal studies, and the implications for humans are unclear. Other risk factors for osteosarcoma include radiation to bone, and this should be considered in evaluating the use of teriparatide in cancer patients. The drug is best avoided in patients with cancer because it increases bone turnover, which may promote propagation of microscopic bone metastases. Teriparatide may be considered for cancer patients with severe osteoporosis and fractures despite the use of bisphosphonates, for whom the mortality risk from fractures is greater than the mortality risk from their cancer.

The use of estrogens to prevent or treat bone loss has fallen out of favor because of concern about stimulation of breast cancer cell growth, even in women with estrogen receptor-negative disease. Most breast cancers are estrogen dependent, so estrogens should be avoided in women with breast cancer. Also recommended are moderation with regard to dietary phytoestrogens and avoidance of dietary supplements that are clearly estrogenic.

Calcitonin salmon may be an option for women with breast cancer and osteoporosis if bisphosphonates and other therapeutic options are not tolerated. Calcitonin salmon is approved by FDA for the treatment (not prevention) of postmenopausal osteoporosis only in women who are more than five years beyond menopause. However, no data for use of the drug to treat cancer treatment-induced bone loss are available.

Prostate cancer. Bone loss in the lumbar spine and hip associated with androgen-deprivation therapy was prevented by use of the bisphosphonate pamidronate or zoledronic acid in small, short-term studies of men with nonmetastatic prostate cancer. In a one-year study of 106 such men, the mean BMD in the lumbar spine increased by 5.6% in men receiving zoledronic acid 4 mg i.v. every three months and decreased by 2.2% in men receiving placebo, a difference that was significant (p < 0.001).

In another randomized study of a single 4-mg i.v. dose of zoledronic acid in 40 men with nonmetastatic prostate cancer who were receiving androgen-deprivation therapy, the mean BMD in the lumbar spine increased by 4.0% in zoledronic acid-treated men and decreased by 3.1% in placebo-treated men (p < 0.001) after one year. The total hip BMD increased by 0.7% in zoledronic acid-treated men and decreased by 1.9% in placebo-treated men (p = 0.004). These findings suggest the feasibility of giving the drug once annually instead of every three months; however, further follow-up is required.

Alendronate 70 mg orally once weekly was evaluated in a randomized, double-blind, placebo-controlled study of 112 men with nonmetastatic prostate cancer who were receiving androgen-deprivation therapy.
therapy. After one year of androgen treatment, BMD increased in the spine by 3.7% and at the femoral neck by 1.6%. After one year of placebo treatment, BMD decreased by 1.4% in the spine and 0.7% at the femoral neck. The differences between treatment groups were significant ($p < 0.001$). Long-term fracture data on the use of alendronate and other bisphosphonates in men with prostate cancer who are receiving androgen-deprivation therapy are not yet available.

Increases in hip and spine BMD were demonstrated with the use of raloxifene in a 12-month, open-label study of 48 men with nonmetastatic prostate cancer who were receiving androgen-deprivation therapy. The mean lumbar spine BMD increased by 1.0% in men treated with raloxifene and decreased by 1.0% in men who did not receive the drug ($p = 0.07$). Total hip BMD increased by 1.1% in raloxifene-treated men and decreased by 2.6% in men who did not receive raloxifene ($p < 0.001$).

Interim results after one year of a Phase III toremifene study of 1392 men with prostate cancer who were receiving androgen-deprivation therapy showed significant improvements in BMD. The lumbar spine BMD increased by 1.6% in the toremifene group and decreased by 0.7% in the placebo group ($p < 0.001$). The total hip BMD increased by 0.7% in the toremifene group and decreased by 1.3% in the placebo group ($p = 0.001$). The femoral neck BMD increased by 0.2% in the toremifene group and decreased by 1.3% in the placebo group ($p = 0.009$). Improvements in lipid profile (decreased total cholesterol, low-density lipoprotein cholesterol, and triglycerides, and increased high-density lipoprotein cholesterol) also were associated with toremifene use. Toremifene is not approved by FDA for the prevention or treatment of osteoporosis in men or women, and further follow-up is needed prior to its incorporation into clinical practice.

The risk for thromboembolism is a concern with the use of SERMs in men with prostate cancer. Therefore, SERMs are not considered first-line agents for the treatment of osteoporosis in this population but are options if bisphosphonates are not tolerated.

As in women with breast cancer, teriparatide is best avoided in men with prostate cancer because of the potential for promoting propagation of microscopic bone metastases and the increased risk for osteosarcoma seen in animal studies. However, teriparatide may be considered for patients with severe osteoporosis and fractures despite the use of bisphosphonates if the mortality risk from fractures is greater than the mortality risk from cancer.

Calcitonin salmon may be an option for men with prostate cancer and osteoporosis if other therapeutic options are not tolerated. However, data on use of the drug to treat cancer treatment-induced bone loss are not available. The drug is not approved by FDA for use in men with osteoporosis.

Investigational therapies

Various drug therapies are under investigation for the management of bone metastases and may theoretically play a role in the management of cancer treatment-induced bone loss and osteoporosis in patients with cancer (Table 2). Many of these therapies are entering or have recently completed Phase I clinical trials, so approval by FDA will not occur any time soon. Of these approaches to bone loss, clodronate and denosumab are by far the closest to approval in the United States.

Clodronate, a bisphosphonate that has been available in Europe and elsewhere, attenuates bone loss associated with chemotherapy-induced ovarian failure. The drug currently is not available in the United States and has a long and storied past. However, ongoing clinical trials are investigating its use as adjuvant therapy for early-stage breast cancer in combination with chemotherapy, endocrine therapy, or both. To my knowledge, submission for approval to the FDA is not imminent.

Denosumab is a fully human monoclonal immunoglobulin G antibody that binds to receptor for activator of nuclear factor $\kappa B$ ligand (RANKL), thereby preventing the differentiation, activation, and maturation of bone-resorbing osteoclasts. The new drug application for denosumab was submitted to FDA in 2009 and may be nearing approval. The efficacy of denosumab 60 mg subcutaneously every six months for managing cancer treatment-induced bone loss was evaluated in two similar randomized, double-blind, placebo-controlled clinical trials. One trial (registered with FDA as 20040135) was conducted in 245 women with breast cancer and osteopenia ($T$-score $-1$ to $-2.5$) who were receiving aromatase inhibitors. The trial lasted four years, with two years of active treatment and two years off treatment. The other trial (registered with FDA as 20040138) was conducted in 1430 men who were receiving androgen-deprivation therapy for prostate cancer. The men were either 70 years of age or older or they were less than 70 years of age and had low bone mass or history of fracture. The trial lasted five years, with three years of active treatment and two years off treatment. The primary endpoint in both studies was change from baseline in lumbar spine BMD, although this change was evaluated after 12 months in the study of women and after 24 months in the study of men. The occurrence of any fracture and the occurrence of new vertebral fractures after 36 months were secondary outcomes only in the study of men. Overall survival was evaluated after 24 months in women and 36 months in men.
Symposis

Bone Loss and Osteoporosis

Table 2.
Investigational Therapies for Management of Cancer Treatment-Induced Bone Loss and Osteoporosis in Patients with Cancer

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate (a bisphosphonate)</td>
<td>Denosumab (a fully human monoclonal antibody that binds RANKL, thereby preventing the differentiation, activation, and maturation of bone-resorbing osteoclasts)</td>
</tr>
<tr>
<td>MMP-7 inhibitors (MMP-7 can process RANKL to a soluble form that promotes osteoclast activation)</td>
<td>Monoclonal antibody CAL (a humanized monoclonal antibody that targets parathyroid hormone-related protein, which promotes bone resorption and is overexpressed in breast and prostate cancers)</td>
</tr>
<tr>
<td>Src inhibitors (Src is involved in signaling cascades that contribute to osteoclast activity)</td>
<td>p38 MAP kinase inhibitors (MAP kinases are involved in various signal transduction pathways that promote osteoclast activity and bone resorption)</td>
</tr>
<tr>
<td>Proteosome inhibitors (proteosome inhibitors are potent stimulators of osteoblast function and inhibitors of osteoclast function through inhibition of RANK)</td>
<td>Proteosome inhibitors (proteosome inhibitors are potent stimulators of osteoblast function and inhibitors of osteoclast function through inhibition of RANK)</td>
</tr>
<tr>
<td>Vitronectin receptor inhibitors (vitronectin receptor is required for adherence of osteoclasts to bone surface)</td>
<td>Vitronectin receptor inhibitors (vitronectin receptor is required for adherence of osteoclasts to bone surface)</td>
</tr>
<tr>
<td>Odanacatib and other cathepsin K inhibitors (cathepsin K is a mediator of bone resorption caused by cancer cells as well as osteoclasts)</td>
<td>Odanacatib and other cathepsin K inhibitors (cathepsin K is a mediator of bone resorption caused by cancer cells as well as osteoclasts)</td>
</tr>
</tbody>
</table>

*p38 MAP kinase; RANKL = receptor for activator of nuclear factor κB ligand; MMP-7 = matrix metalloproteinase-7; MAP = mitogen-activated protein; RANK = receptor for activator of nuclear factor κB.

*Entering or recently completed Phase I trials.

In the study of women, the lumbar spine BMD increased from baseline by 4.8% with denosumab and decreased by 0.7% with placebo after 12 months, \( p < 0.0001 \).53 Similarly, in the study of men, the lumbar spine BMD increased by 5.6% with denosumab and decreased by 1.0% with placebo after 24 months \( p < 0.0001 \).53 After 36 months, the frequency of any fracture was 5.2% in denosumab-treated men and 7.2% in placebo-treated men, representing a nonsignificant 28% relative risk reduction.53 The frequency of new vertebral fractures was 1.5% in denosumab-treated men and 3.5% in placebo-treated men, representing a significant 62% relative risk reduction \( p = 0.0125 \).53 The short duration of follow-up might have contributed to these findings. Therefore, further follow-up is required before definitive conclusions can be drawn.

The potential for new malignancies is a concern with the use of denosumab. Carcinogenicity studies have not been performed because of a lack of an animal model, and agents such as denosumab are likely to be used for many years in patients without cancer for the indication of osteoporosis.54 In an analysis of safety data from more than 8000 participants in clinical trials of denosumab for postmenopausal osteoporosis, the rate of any malignant neoplasm was 4.7% with denosumab and 4.2% with placebo. Although this difference was not statistically significant, the numeric differences between certain cancer types are somewhat concerning; there were higher rates of gastrointestinal (GI), breast, and female reproductive cancers in denosumab-treated subjects. Of the 192 malignant neoplasms identified in the 4050 denosumab-treated patients, 35 were gastrointestinal, 35 were breast, and 21 were female reproductive cancers. The corresponding findings in the 4041 placebo-treated subjects were 24, 29, and 9, respectively. None of these differences was significant, but conservative monitoring is necessary because of the serious nature of this adverse effect.

The rate of metastatic events in study participants who received at least one dose of denosumab was part of the safety analysis in the cancer treatment-induced bone loss studies. In the study of women with breast cancer, metastatic events occurred in 7.2% of denosumab-treated women and 4.0% of placebo-treated women.54 In the study of men with prostate cancer, metastatic events occurred in 8.2% of denosumab-treated subjects and 5.5% of placebo-treated subjects.54 These differences are not significant. Nevertheless, the possibility of disease progression in patients with cancer who receive denosumab raises concerns about the usefulness of the drug for managing cancer treatment-induced bone loss. Clinical trials in patients with bone metastases are in progress. Further follow-up is required for definitive conclusions to be drawn, and it is not clear how the FDA will react to this information. The FDA has requested more information from the manufacturer of denosumab, though more clinical trials were not requested. A risk evaluation and mitigation strategy (REMS) will likely be required if the drug is approved.

Pharmacist’s role

Bone health usually receives low priority among the many problems that oncology professionals need to address with their patients. Large numbers of cancer survivors obtain health care from non-oncologists,
whose awareness of cancer treatment-induced bone loss may be limited. Health-system pharmacists can make a valuable contribution to patient care by assisting oncologists, primary care physicians, and other members of the health care team in screening patients with a history of cancer for bone loss and making drug therapy recommendations to the health care team to address the problem.

Pharmacists (especially those in outpatient clinic and retail pharmacy settings) also can play an important role in managing cancer treatment-induced bone loss and osteoporosis by counseling patients about modifiable risk factors for osteoporosis (increasing calcium and vitamin D intake and physical activity and reducing smoking and alcohol use) and the proper use of drug therapies to improve bone health. Pharmacists might refer patients to appropriate facilities to assist with risk factor modification (e.g., smoking cessation programs).

Application to patient cases

The case of patient TJ illustrates the screening, assessment, and therapeutic decision-making processes used by pharmacists for a patient with breast cancer. The case of patient case SM illustrates these processes for a patient with prostate cancer.

**Patient TJ.** TJ is a 62-year-old black woman who presents to the clinic for follow-up of community-acquired pneumonia secondary to infection with the H1N1 influenza virus. She was discharged from the hospital two weeks ago and is a new patient to your clinic. Her past medical history includes hypertension diagnosed 5 years ago and breast cancer diagnosed 10 years ago. Currently, she has no evidence of malignant disease. Her family history is noncontributory (i.e., there is no history of breast cancer in her family). TJ takes hydrochlorothiazide 25 mg orally once daily for her hypertension. She occasionally drinks a glass of wine with dinner, but she does not smoke cigarettes or abuse intravenous drugs. TJ’s vital signs at the clinic are as follows:

- **Systolic/diastolic blood pressure:** 134/74 mm Hg
- **Weight:** 125 lb
- **Height:** 5’3”

TJ may be at risk for osteoporosis and fractures because of her advanced age and other risk factors. It is important to ascertain whether TJ received chemotherapy, endocrine therapy (e.g., tamoxifen, aromatase inhibitors), or both and her ovarian function (i.e., whether her cessation of menses was spontaneous or surgically or medically induced as a result of oophorectomy or the use of LHRH agonists). Obtaining this information can pose a challenge for clinicians when a patient’s disease manifested itself as long ago as in TJ’s case. Fortunately, TJ’s medical records are complete, and she remembers many of the details clearly. When TJ was diagnosed with breast cancer at the age of 52, which is relatively young, she underwent surgery consisting of a lumpectomy with sentinel lymph node biopsy (SNLB). This biopsy procedure involves the injection of dye around the primary tumor and evaluation of only those lymph nodes to which the dye drains. The use of SNLB often avoids the need for full axillary lymph node dissection, and it is now considered the standard of care. TJ also underwent oophorectomy because of ovarian cysts; the oophorectomy was performed at the same time as the lumpectomy and SNLB for the sake of convenience (i.e., while she was already under anesthesia). TJ received four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel. She then received the aromatase inhibitor anastrozole for five years. TJ had been menstruating at the time of her breast cancer diagnosis and treatment, but the oophorectomy induced an early menopause.

In assessing TJ’s risk for osteoporosis and fractures, the presence of the risk factors in Table 1 should be determined. She should be asked questions about her use of nonprescription medications (particularly calcium-containing antacids, which she does not take). Dietary intake of calcium and vitamin D, physical activity, and exposure to sunlight also should be ascertained. Exposure to sunlight activates vitamin D, which promotes GI absorption of calcium. TJ drinks several glasses of milk and calcium-fortified orange juice every day. She began walking on a daily basis when she retired this year and is exposed to sunshine during her daily walks.

Whether TJ has been screened for osteoporosis using a DXA scan and other clinical assessments is another piece of vital information to obtain. According to the NCCN task force report on bone health in cancer care, TJ’s fracture risk should have been assessed by obtaining a bone-related history and physical, performing DXA scans, and using the FRAX fracture risk assessment tool from the WHO when she began anastrozole and experienced early menopause due to oophorectomy. This assessment was never done, but it is performed now with the following results:

- **T-scores:** –2.5 right femur and –2.4 left femur
- **FRAX 10-year risk of major osteoporotic fracture:** 5.2%
- **FRAX 10-year risk of hip fracture:** 1.1%

According to the NCCN task force report on bone health in cancer care, pharmacologic therapy for osteoporosis should be strongly considered for TJ because her T-scores are lower than –2.0. With her right femur T-score of –2.5, TJ meets the WHO diagnostic criteria for osteoporosis.

Bisphosphonates are the treatment of choice for osteoporosis in patients such as TJ with a history of breast...
cancer and use of an aromatase inhibitor. The bisphosphonate with the best data in this patient population is zoledronic acid. The drug might also reduce TJ’s risk of cancer recurrence although this effect requires confirmatory trials.18

TJ has no history of GI disorders that would be of concern in choosing to use a bisphosphonate, and she probably does not have severe renal impairment. Although TJ has a history of cancer, her risk of osteonecrosis of the jaw is minimal. Like other patients with a history of cancer and use of chemotherapy, TJ should consider undergoing dental examination with appropriate preventive dentistry prior to treatment with bisphosphonates, and she should avoid invasive dental procedures if possible during bisphosphonate treatment.

Although raloxifene might reduce TJ’s risk for a secondary breast cancer, the drug is not a good choice for treating her osteoporosis because it increases the risk for thromboembolism.34 Moreover, no data are available to support the use of raloxifene for prevention of breast cancer in patients such as TJ, who received five years of therapy with an aromatase inhibitor five years ago.

Calcium and vitamin D supplementation are recommended in conjunction with prescription medication to treat osteoporosis in patients such as TJ who do not have bone metastases. However, if TJ did have bone metastases, calcium supplementation should be implemented cautiously because of the risk of hypercalcemia in patients with bone metastases.

**Patient SM.** SM is a 75-year-old Caucasian man who returns to the clinic for follow-up of his hypertension. He is nonadherent to his treatment regimen and has missed several appointments over the past few years. SM’s past medical history also includes prostate cancer diagnosed five years ago. He reports that he has taken lisinopril 5 mg orally once daily for five years for his hypertension. His mother had osteoporosis and bilateral hip fractures. SM is a long-time cigarette smoker (two packs per day for 40 years), and he occasionally consumes alcohol, although he does not report abusing intravenous drugs. His vital signs at the clinic are as follows:

- Systolic/diastolic blood pressure: 148/90 mm Hg
- Weight: 225 lb
- Height: 6’1”

SM may be at risk for osteoporosis and fractures because of his prostate cancer, advanced age, heavy cigarette smoking, maternal history of osteoporosis and hip fractures, and other risk factors. It is important to ascertain whether SM received chemotherapy with or without corticosteroids and androgen-deprivation therapy (an LHRH agonist or orchietomy) and the status of his malignancy (i.e., whether there is any evidence of disease). LHRH agonists may not appear on medication lists because they are given infrequently (e.g., once every three or four months). Some men are reluctant to remember and discuss orchietomy; they may not reveal information about this surgery unless specifically asked.

SM’s prostate cancer was locally advanced when it was diagnosed five years ago. He has been receiving androgen-deprivation therapy with the LHRH agonist leuprolide administered by injection every three months since then with no signs of metastatic disease. Given SM’s history of failure to keep clinic appointments, he may have missed appointments for leuprolide injections. His slightly elevated blood pressure readings suggest nonadherence to lisinopril therapy. Measuring testosterone levels might be helpful for ascertaining adherence to LHRH agonist therapy in a patient such as SM. Because androgen-deprivation therapy increases the risk for osteoporosis, failure to adhere to LHRH agonist therapy would be beneficial for bone health, although it could allow progression of malignancy. As measured now at the clinic, SM’s testosterone level is adequately suppressed (42 ng/mL), indicating that he has received at least some of his leuprolide injections.

Whether SM has been screened for osteoporosis using a dual-energy X-ray absorptiometry (DXA) scan and other clinical assessments is another piece of vital information to obtain. Osteoporosis typically is thought of as a woman’s disease, and awareness of the need to screen for the disease has been limited until recently among oncologists who care for prostate cancer patients. Bone loss has become an important issue among prostate cancer survivors. According to the NCCN task force report on bone health in cancer care, SM’s fracture risk should have been assessed by obtaining a bone-related history and physical, performing a DXA scan, and using the FRAX fracture risk assessment tool from the WHO when he began leuprolide therapy.14,15 This assessment was never done, but it is performed now with the following results:

- T-scores: –1.8 right femur and –1.6 left femur
- FRAX 10-year risk of major osteoporotic fracture: 22%
- FRAX 10-year risk of hip fracture: 18%

According to the NCCN task force report, pharmacologic therapy for low bone mass should be strongly considered for SM.14 He meets the WHO diagnostic criteria for osteopenia (not osteoporosis) on the basis of his T-scores, and his FRAX 10-year risk of major osteoporotic fracture exceeds 20% and his FRAX 10-year risk of hip fracture exceeds 3%.3,14,54

A bisphosphonate, such as alendronate, pamidronate, or zoledronic acid, would be a good choice for SM. These drugs have been shown to improve or prevent loss of spine and hip BMD in patients such as SM with

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**SYMPOSIUM Bone loss and osteoporosis**

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nonmetastatic prostate cancer who are receiving androgen-deprivation therapy.39-42 Adherence, out-of-pocket costs, and tolerance are all issues to be discussed with SM in order to optimize the therapeutic choice for this individual. Because of his lack of compliance with other past therapies, the clinician should openly discuss this individual. Because of his lack of costs, and tolerance are all issues to be discussed with SM in order to planning deprivation therapy.43 The use of cancer who are receiving androgen-deprivation and spine BMD in men such as to promotes improvements in early detection and treatment of osteoporosis in men with prostate cancer.45 Raloxifene and toremifene are not approved by FDA for the prevention or treatment of osteoporosis in men.67

Calcium and vitamin D supplementation are recommended in conjunction with prescription medication to prevent bone loss in patients such as SM who do not have bone metastases. If SM did have bone metastases, calcium supplementation should be implemented cautiously because of the risk of hypercalcemia in patients with bone metastases. SM also should be counseled about the importance of smoking cessation, exercise, and limiting his intake of alcoholic beverages.

Conclusion
Large numbers of breast or prostate cancer survivors are alive because of improvements in early detection and treatment of these malignancies. Many of these survivors have or are at risk for osteoporosis or osteopenia because of cancer treatment-induced bone loss and other risk factors. Various drug therapies are available or in development to manage osteoporosis and osteopenia in cancer patients. Health-system pharmacists can plan an important role in screening for osteoporosis and osteopenia and promoting bone health in patients with breast or prostate cancer.

References
29. Actonel package insert. Cincinnati, OH:
SYMPOSIUM Bone loss and osteoporosis

Procter & Gamble Pharmaceuticals, Inc.; 2009 Aug.
Learning Objectives

After studying these articles, the reader should be able to

1. Describe the epidemiology, morbidity, mortality, and risk factors associated with osteoporosis and osteoporosis-related fractures in the United States.
2. Identify patients who are candidates for bone mineral density testing and use the results to determine whether treatment is indicated to reduce the risk for osteoporosis-related fractures.
3. Explain the factors that contribute to a bone healthy lifestyle in postmenopausal women with or at risk for osteoporosis, including current recommendations for adequate calcium and vitamin D intake.
4. Identify the considerations in selecting drug therapy for the prevention or treatment of postmenopausal osteoporosis.
5. Discuss risk factors for bone loss, osteoporosis, and fractures in patients with breast and prostate cancer, as well as the approach to risk assessment in patients with these malignancies.
6. Explain the process for managing cancer treatment-induced bone loss or osteoporosis in patients with a history of breast or prostate cancer, including screening for bone loss and osteoporosis, determining whether drug therapy is indicated, and identifying appropriate pharmacologic options.

Self-assessment questions

For each question there is only one best answer.

1. Which of the following statements about the prevalence and impact of osteoporosis and osteoporosis-related fractures is correct?
   a. Vertebral fractures are associated with up to a 20% increase in mortality the year after the fracture.
   b. The prevalence of osteoporosis and related fractures is higher in women than in men, but the impact of the disease is great in both sexes.
   c. The prevalence of osteoporosis and related fractures is higher in men than in women, but the impact of the disease is less in men than in women.
   d. Hip fractures are the most common type of osteoporosis-related fracture.

2. Which of the following statements about the rates of screening for and treatment of osteoporosis in the United States and evidence of potential benefits is correct?
   a. Rates of screening and treatment are adequate despite a lack of documented evidence of potential benefits.
   b. Rates of screening and treatment are inadequate despite ample evidence of potential benefits.
   c. Rates of screening and treatment are inadequate because of a lack of documented evidence of potential benefits.
   d. Rates of screening and treatment are inadequate despite a lack of documented evidence of potential benefits.

3. Which of the following is considered a risk factor for osteoporosis and fractures in postmenopausal women and men age 50 and older?
   a. Corticosteroid use.
   b. Hypertension.
   c. Obesity.
   d. Hepatic impairment.

4. Which of the following statements regarding T-scores is correct?
   a. T-scores describe the bone mineral density compared to the expected normal for the patient's age and sex.
   b. T-scores may be used alone to predict the absolute risk of an osteoporotic fracture.
   c. T-scores should be used with age and other risk factors to predict osteoporotic fracture risk.
   d. T-scores account for over 95% of bone strength.

5. For which of the following patients should bone mineral density testing be performed?
   a. A 30-year-old woman with a prior fracture and risk factors for osteoporosis.
   b. A 40-year-old woman with no prior fractures or risk factors for osteoporosis.
   c. A 40-year-old man with no prior fractures or risk factors for osteoporosis.
CONTINUING EDUCATION

6. Which of the following is the appropriate diagnosis for a patient more than 50 years of age with a T-score of –2.0 at the left femoral neck as measured by central dual-energy X-ray absorptiometry according to the World Health Organization diagnostic criteria?
   a. Normal.
   b. Osteopenia.
   c. Osteoporosis.
   d. Severe osteoporosis.

7. For which of the following patients is initiation of treatment indicated to reduce the risk for osteoporosis-related fractures according to National Osteoporosis Foundation recommendations?
   a. A woman with a T-score of –1.2 at the femoral neck or spine, no hip or vertebral fracture, and a 10-yr probability of hip fracture of 1%.
   b. A woman with a T-score of –2.2 at the femoral neck or spine, no hip or vertebral fracture, and a 10-yr probability of hip fracture of 2%.
   c. A woman with a T-score of –2.2 at the femoral neck or spine, a vertebral fracture, and a 10-yr probability of hip fracture of 4%.
   d. A woman with a T-score of –2.2 at the femoral neck or spine, no hip or vertebral fracture, and a 10-year probability of a major osteoporosis-related fracture of 4%.

8. Which of the following contributes to vitamin D deficiency and an increased risk for osteoporosis in postmenopausal women?
   a. Excessive caffeine intake.
   b. Loss of estrogen after menopause.
   c. Inadequate exposure to sunlight.
   d. Insufficient dietary calcium intake.

9. Which of the following daily intakes of elemental calcium and vitamin D currently are recommended by the National Osteoporosis Foundation for postmenopausal women 50 years of age or older?
   a. Elemental calcium ≥ 1000 mg and vitamin D 400–800 units.
   b. Elemental calcium ≥ 1200 mg and vitamin D 800–1000 units.
   c. Elemental calcium ≥ 1200 mg and vitamin D 1000–2000 units.
   d. Elemental calcium ≥ 1200 mg and vitamin D 2000–4000 units.

10. Which of the following osteoporosis drug therapies has estrogen agonist activity in bone?
    a. Bisphosphonates.
    b. Calcitonin salmon.
    c. Raloxifene.
    d. Teriparatide.

11. Which of the following considerations are potential limitations in the use of teriparatide to treat osteoporosis in postmenopausal women?
    a. Risk for venous thromboembolism and subcutaneous (s.c.) route of administration.
    b. Risk for osteosarcoma and need for refrigerated storage.
    c. Risk for stroke and route of administration.
    d. Risk for esophageal ulcers and need for refrigerated storage.

12. Which of the following osteoporosis drug therapies is preferred (i.e., considered first-line therapy) for postmenopausal women?
    a. Oral bisphosphonates.
    b. Calcitonin salmon.
    c. Raloxifene.
    d. Teriparatide.

13. Which of the following is the most direct potential advantage of administering oral osteoporosis drug therapy on an infrequent (e.g., yearly or monthly) basis instead of daily?
    a. Greater efficacy.
    b. Greater tolerability.
    c. Improved adherence.
    d. Lower cost.

14. Which of the following is a recent trend in breast cancer and prostate cancer survival and concerns about cancer treatment-induced bone loss and osteoporosis in these patient populations?
    a. Survival has improved in women with breast cancer and men with prostate cancer, but cancer treatment-induced bone loss and osteoporosis are concerns primarily in women with breast cancer.
    b. Survival has improved in women with breast cancer and men with prostate cancer, and cancer treatment-induced bone loss and osteoporosis are concerns in both women with breast cancer and men with prostate cancer.
    c. Survival has improved in women with breast cancer but not in men with prostate cancer, so cancer treatment-induced bone loss and osteoporosis are concerns primarily in women with breast cancer.
    d. Survival has improved in men with prostate cancer but not in women with breast cancer, so cancer treatment-induced bone loss and osteoporosis are concerns primarily in men with prostate cancer.

15. Which of the following cancer therapies is the most common cause of bone loss in women with breast cancer?
    a. Aromatase inhibitors.
    b. Corticosteroids.
    c. Selective estrogen receptor modulators.
    d. Radiation therapy.

16. According to the National Comprehensive Cancer Network (NCCN) task force report on bone health in cancer care, which of the following conditions in a patient with cancer is sufficient to warrant assessment of bone health and fracture risk using a bone-related history and physical examination, dual-energy X-ray absorptiometry scanning, and the FRAX fracture risk assessment tool from the World Health Organization?
    a. Age ≥ 65 years.
    b. Female sex.
17. Which of the following recommendations about pharmacologic therapy for low bone mass in patients with cancer and a T-score between −1.5 and −2.0 was made in the NCCN task force report on bone health in cancer care?
   a. It should be considered.
   b. It should be strongly considered.
   c. It should not be considered unless bone metastases are present.
   d. It should not be considered under any circumstances.

18. Which of the following therapies might prevent disease recurrence, as well as improve or maintain bone mineral density, in a woman with osteoporosis and a history of breast cancer?
   a. Calcitonin salmon.
   b. Estrogen.
   c. Teriparatide.
   d. Zoledronic acid.

19. Which of the following risks is a potential limitation in the use of raloxifene for managing cancer treatment-induced bone loss and osteoporosis in patients with breast or prostate cancer?
   a. Osteosarcoma.
   b. Osteonecrosis of the jaw.
   c. Propagation of microscopic bone metastases.
   d. Thromboembolism.

20. Which of the following investigational therapies with potential applications in the management of postmenopausal osteoporosis and cancer treatment-induced bone loss and osteoporosis in patients with cancer is a fully human monoclonal immunoglobulin G antibody that binds to receptor activator of nuclear factor κB ligand (RANKL)?
   a. Clodronate.
   b. Denosumab.
   c. Monoclonal antibody CAL.
   d. Odanacatib.

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