Therapeutic Options in the Prevention and Treatment of Postmenopausal Osteoporosis

Hosam K. Kamel, MD, MPH, FACP, AGSF, FGSA
Mary Beth O’Connell, PharmD, BCPS, FASHP, FCCP
Deborah T. Gold, PhD
Deborah T. Gold, PhD, is an associate research professor of medical sociology in the departments of Psychiatry and Behavioral Sciences, Sociology, and Psychology: Social and Health Sciences, Duke University Medical Center, Durham, North Carolina. She is a senior fellow in the Duke Center for the Study of Aging and Human Development, a faculty affiliate of the Duke Women’s Studies Program. Gold is a member of the Faculty Advisory Committee of the Graduate Liberal Studies Program and also directs the Postdoctoral Research Training Program in Aging, the Leadership in an Aging Society Program, and the Undergraduate Human Development Program at Duke.

Gold received her AB degree from the University of Illinois; MEd degree from National College of Education, National-Louis University; and PhD in human development and social policy from Northwestern University. She completed a postdoctoral fellowship in medical sociology and gerontology at the Duke Aging Center. A fellow of the Gerontological Society of America, Gold has chaired its Membership and Research, Education, and Practice committees; she was recently elected chair of its Behavioral and Social Sciences section. Gold is also a trustee of the National Osteoporosis Foundation (NOF) and chair of its Education Committee; she served on the Development Committee for NOF’s Physician’s Guidelines and its Rehabilitation Guidelines. She was cochair of the NOF 6th International Symposium on Osteoporosis in 2005 and will chair the next such meeting in 2007. Gold is also a member of the Governor’s Task Force on Osteoporosis for the state of North Carolina and was a coordinating author on Bone Health and Osteoporosis: A Surgeon General’s Report (2004). Her current research focuses on the psychosocial aspects of chronic illnesses in late life, with the majority of research focused on osteoporosis. She has published extensively on metabolic bone disease.

Hosam K. Kamel, MD, MPH, FACP, AGSF, FGSA, is director, Geriatrics and Extended Care, St. Joseph’s Mercy Health Center, Hot Springs, Arkansas, and is a member of the faculty in the Department of Geriatrics, University of Arkansas for Medical Sciences. He is the current president of the Arkansas Medical Directors Association and serves as cochair of the Steering Committee of the Clinical Practice Guidelines Project, American Medical Directors Association.

He completed medical school at Kuwait University School of Medicine and earned a master’s of public health degree at the Medical College of Wisconsin. He also completed a 2-year National Institutes of Health-funded Clinical Research Scholars Award (2001-2003) at the Health Policy Institute at the Medical College of Wisconsin. Kamel has been elected a fellow of the American College of Physicians, the American College of Nutrition, the American Geriatric Society, and the Gerontological Society of America. He has also been elected a full member of the SIGMA XI honor scientific research society.

Kamel has been the editor-in-chief of Internet Journal of Geriatrics and Gerontology since 2003 and served or currently serves on the editorial boards of the Journal of the American Medical Directors Association, Annals of Long Term Care, and Journal of Gerontology Medical Sciences. He has coauthored 165 scientific publications (books, book chapters, abstracts, and papers) and 7 national clinical practice guidelines, including the osteoporosis clinical practice guidelines by the American Medical Directors Association (2003).

Mary Beth O’Connell, PharmD, BCPS, FASHP, FCCP, is an associate professor, Pharmacy Practice Department, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan. She received her bachelor of science in pharmacy degree from Wayne State University and PharmD degree from the University of Minnesota. She completed an ASHP-accredited residency at Harper Hospital, Detroit, Michigan, and a research fellowship at the Drug Evaluation Unit, Minneapolis, Minnesota. Her teaching, practice, and research focus on geriatric pharmacotherapy, with an emphasis on prevention and treatment of osteoporosis. She is a fellow of the American Society of Health-System Pharmacists and the American College of Clinical Pharmacy.
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Osteoporosis is a major public health issue. It is an age-related disease that affects an estimated 10 million Americans. Another 34 million Americans are at risk for osteoporosis because of a low bone mass. By the year 2050, the number of Americans older than 65 years is expected to double, reaching 69 million. Therefore, the impact of osteoporosis is expected to increase dramatically in the United States in the coming decades.

Eighty percent of patients with osteoporosis are women. The risk for osteoporosis increases after menopause, with 1 in 5 white postmenopausal women affected. Whites are the racial group for which the most data on osteoporosis are available, but other racial and ethnic groups also are at risk.

Osteoporosis is associated with an increased risk of fractures, which can lead to chronic pain, deformity, disability, and death. One of every 2 women and 1 of every 4 men over the age of 50 years will experience an osteoporotic fracture at some time in their remaining lifetime. Osteoporosis is responsible for more than 1.5 million fractures annually, including more than 300,000 hip fractures, 700,000 vertebral fractures, 250,000 wrist fractures, and 300,000 fractures at other sites.

Vertebral fractures, the most common type of fracture, often are accompanied by a loss of height, chronic pain, disfigurement (the characteristic stooped posture from kyphosis), and functional deficits. Hip fractures are less common than vertebral fractures, but they are more devastating. Up to 20% of patients with a hip fracture die within 1 year after the fracture. More than 30% of patients with hip fractures are permanently disabled, and many patients require help with activities of daily living and require long-term nursing care. The risk of another hip fracture is 4-fold higher in persons who already have suffered one hip fracture than in people without a history of hip fractures.

Osteoporosis has an enormous economic impact in the United States because of the loss of productivity and independence after hip fractures. The health care costs for osteoporosis were estimated at $13.8 billion in 1995. The direct costs of osteoporotic hip fractures alone amounted to $18 billion in 2002. The cost of osteoporosis in the United States could reach as much as $240 million by 2050.

Evaluation and treatment of osteoporosis are inadequate, leading to preventable fractures. Two of cases of osteoporosis go undiagnosed. Only 1 in 7 women with osteoporosis receives treatment. Furthermore, after sustaining a hip fracture, most patients do not receive bone density measurements or adequate therapy to prevent subsequent fractures. Research has shown that minimal effort to improve osteoporosis evaluation and treatment can have a dramatic impact on patient outcomes.

Community pharmacists have measured heel bone density and counseled patients effectively on positive lifestyle modifications.
Adherence to osteoporosis medications often is poor because of adverse effects, forgetfulness, a silent disease, or other reasons. Medication nonadherence can compromise patient outcomes, leading to increased health care utilization and costs.

Osteoporosis has been the focus of public and private initiatives because of its large impact on the U.S. economy and quality of life of Americans. The years 2002-2011 have been designated the Bone and Joint Decade in the United States as part of an initiative to improve public awareness, patient education, research, and the diagnosis and treatment of osteoporosis by developing new collaborative partnerships between patient advocacy groups, musculoskeletal associations, care providers, researchers, and industry.

In 2004, the Office of the Surgeon General released its first major report on bone health and osteoporosis. In 2004, the National Committee for Quality Assurance adopted a new Health Plan Employer Data and Information Set (commonly referred to as HEDIS) performance measure requiring women aged 67 years and older who have had a fracture to undergo evaluation by dual energy X-ray absorptiometry and receive a bisphosphonate if appropriate within 6 months of the fracture.

In January 2006, as part of its quality improvement efforts, the Centers for Medicare & Medicaid Services launched the Physician Voluntary Reporting Program (PVRP) to improve the health and function of Medicare beneficiaries by preventing chronic disease complications, avoiding preventable hospitalizations, and improving the quality of care delivered. The program involves several quality initiatives in a variety of settings (e.g., hospitals, skilled nursing facilities, home health care agencies, and dialysis centers). Physician participation is voluntary; physicians who choose to participate will gather and submit data about the quality of care provided to Medicare beneficiaries and receive feedback on their performance. The program consists of 36 evidence-based, clinically valid measures that were part of guidelines endorsed by physicians and their medical specialty societies. A smaller core starter set of 16 measures will be used initially to reduce the reporting burden for physicians. Assessment of elderly patients for falls (a major cause of fractures) is one of the 16 core starter set measures. Several of the 20 quality measures that will not be assessed initially as part of the PVRP address postmenopausal osteoporosis.

These public and private efforts to reduce the impact of osteoporosis on Americans have the potential to improve quality of life and reduce health care utilization and costs. The expected growth in the population of elderly Americans at risk for osteoporosis and other chronic illnesses in the coming decades provides an impetus to devise strategies to prevent avoidable morbidity and use limited health care resources wisely.

The first article in this supplement discusses the etiology and diagnosis of postmenopausal osteoporosis and nonprescription interventions used to prevent or manage the disease. In the second article, prescription drug therapies for preventing and treating postmenopausal osteoporosis and some pharmacoeconomic studies are described in detail. The third article defines medication adherence and explains the limitations of direct and indirect methods for its assessment. Possible reasons for unintentional and intentional nonadherence to medications used for chronic illnesses are suggested, and the impact of nonadherence to osteoporosis drug therapies on patient outcomes and health care costs is quantified. Considerations in devising individualized strategies for improving adherence also are discussed.

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Postmenopausal Osteoporosis: Etiology, Current Diagnostic Strategies, and Nonprescription Interventions

HOSAM K. KAMEL, MD, MPH, FACP, AGSF, FGSA

ABSTRACT

OBJECTIVE: To describe the etiology, diagnosis, and nonprescription interventions for the prevention and treatment of postmenopausal osteoporosis.

BACKGROUND: Osteoporosis affects more than 20 million individuals in North America and is responsible for more than 1.5 million fractures in the United States. About 50% of white women in the United States will have an osteoporotic fracture during their lifetime.

SUMMARY: Postmenopausal osteoporosis is the result of estrogen deficiency, which results in up-regulation of several cytokines and excessive bone resorption. Various bone mineral density (BMD) testing methods are available, but the World Health Organization based the diagnosis of postmenopausal osteoporosis on the presence of a BMD T-score that is 2.5 standard deviations or greater below the mean for young women as assessed by dual-energy X-ray absorptiometry (DXA) at the hip, spine, and midradius. Ensuring adequate calcium and vitamin D intake is the cornerstone of any regimen aimed at preventing or treating postmenopausal osteoporosis. Other nonpharmacologic measures address modifiable risk factors for the disease and include exercise, smoking cessation, reducing consumption of caffeine and alcohol, and avoiding medications known to decrease bone mass.

CONCLUSIONS: Postmenopausal osteoporosis is the result of estrogen deficiency and excessive bone resorption. Ensuring intake combined with lifestyle changes to address modifiable risk factors for the disease may help in the prevention and treatment of this condition.

KEYWORDS: Postmenopausal osteoporosis, Bone, Estrogen, Calcium

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until recently, osteoporosis was defined as a condition of generalized skeletal fragility in which bone strength is sufficiently weak that fractures occur with minimal trauma, often no more than is applied by routine daily activity. The diagnosis of osteoporosis was not made until a fracture occurred, when it was too late to intervene.

Osteoporosis currently is defined as a skeletal disorder characterized by compromised bone strength, predisposing to fractures. Bone strength reflects both bone density and bone quality. Bone density usually is assessed by noninvasive means using various measures of bone mineral density (BMD, i.e., the grams of mineral per area or volume). Bone quality reflects bone architecture (strength, connectivity), turnover (i.e., replacement), accumulated damage (e.g., microfractures), and mineralization. Bone quality usually is not assessed in clinical practice because it currently involves a bone biopsy, which is an invasive method. The incidence of fractures is an indirect measure of bone quality. The U.S. Food and Drug Administration (FDA) now requires data demonstrating a favorable impact on fracture incidence for approval of drugs to prevent or treat osteoporosis, although an impact on BMD sufficed for drug approval years ago.

Etiology

Bone undergoes a continuous remodeling process (i.e., replacement) involving resorption of old bone by osteoclasts and formation of new bone by osteoblasts. The activity of osteoclasts and osteoblasts ordinarily is balanced and regulated by physical factors and hormonal influences. Osteoporosis is characterized by an imbalance between osteoclast and osteoblast activity and a rate of bone resorption that exceeds the rate of bone formation, resulting in bone loss and skeletal fragility.

Osteoporosis may be primary or secondary to an identifiable cause (i.e., a drug, disease, or condition). Most cases of osteoporosis are primary, especially in the elderly. Approximately 20% of women and 40% of men with osteoporosis have a secondary cause (Table 1).

Primary osteoporosis includes type I (postmenopausal) osteoporosis and type II (senile) osteoporosis. Postmenopausal osteoporosis is the result of estrogen deficiency, which results in up-regulation of several cytokines and excessive bone resorption. It affects women disproportionately, with a 6:1 female-to-male ratio, usually at an age of 51 to 75 years. Bone loss and fractures in postmenopausal osteoporosis primarily involve trabecular bone (i.e., interior porous bone) in the vertebrae and distal radius (i.e., forearm).

Type II osteoporosis usually affects individuals older than 70 years and twice as many women as men. Bone loss typically involves both trabecular and cortical (i.e., outer) bone on the long bones, causing fractures of the femoral neck (i.e., hip), proximal
Type II osteoporosis results from an age-related vitamin D deficiency, which leads to hypocalcemia, a compensatory increase in parathyroid hormone release, and bone resorption.

The risk factors for osteoporosis in postmenopausal women are listed in Table 2. An increased risk is associated with a thin build. Weight gain appears to protect against bone loss in elderly women.

Risk factors for hip fracture were determined in 9,516 white women aged 65 years or older who had no history of hip fracture and were followed for an average of 4.1 years. There were 192 hip fractures in this group, and many of the risk factors identified (e.g., a personal history of any fracture after the age of 50, a maternal history of hip fracture, poor health, a history of hyperthyroidism, tachycardia at rest, high caffeine consumption, low bone mass or BMD) are similar to those in Table 2. Some risk factors for hip fracture reflect a high risk for falls (e.g., a lack of exercise, the use of anticonvulsants or long-acting benzodiazepines, the inability to rise from a chair without using the arms, poor depth perception).

**Diagnosis**

The diagnosis of osteoporosis is based on assessment of BMD. Health Care Financing Administration (now called Centers for Medicare & Medicaid Services) regulations that became effective in 1998 provide for uniform coverage of BMD measurements in the Medicare population using any procedure approved by the FDA. Testing is indicated for estrogen-deficient women who are at clinical risk for osteoporosis, individuals with vertebral abnormalities, persons receiving long-term glucocorticoid therapy, patients with primary hyperparathyroidism, and patients receiving an osteoporosis drug therapy approved by the FDA. Testing may be performed once every 2 years, although more frequent testing is permitted if a physician considers it medically necessary.

Assessing BMD by dual energy X-ray absorptiometry (DXA) scans at the hip and spine, also known as central DXA, is the gold standard method for diagnosing osteoporosis. Central DXA scans involve low exposure to radiation and are easy to perform, even if the patient is bedridden or has problems with mobility. Patients need not undress for the procedure.

Portable instruments can be used to assess BMD at peripheral sites such as the forearm, finger, or heel. Examples of such devices include peripheral DXA scans, heel ultrasound, and single-energy X-ray absorptiometry (SXA) scans. While peripheral devices have the advantages of lower cost and portability over central DXA machines, they are less reliable because they can produce false negative results, and they cannot be used to follow BMD changes over time. Further, the WHO diagnostic criteria for osteoporosis by T-score were based on central DXA measurements, and the threshold was not validated for peripheral BMD measurements. Peripheral BMD measurement devices can be used for screening, but central DXA is required for a definitive diagnosis. BMD usually is reported as a T-score or a Z-score. The T-score is the difference between the individual's BMD and the expected BMD for a “young, normal” adult of the same sex, expressed as the number of standard deviations below the mean. The Z-score compares the individual's BMD with the average BMD for people of the same age and sex. A T-score of -1 or higher (i.e., a BMD within 1 standard deviation lower than that expected for a young, normal adult of the same sex) is considered normal. A T-score between -1 and -2.5 is considered osteopenia, and a T-score of -2.5 or lower (i.e., 2.5 or more standard deviations below the expected BMD) is considered osteoporosis. Patients with a T-score of -2.5 or lower and a history of one or more fragility fractures have what is referred to as established or severe osteoporosis.

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**TABLE 1** Common Causes of Secondary Osteoporosis*

- Hypogonadism (men)
- Chronic glucocorticoid therapy
- Hyperparathyroidism
- Thyrotoxicosis
- Malnutrition
- Malabsorption
- Chronic immobilization
- Rheumatoid arthritis
- Alcoholism
- Vitamin D deficiency

* Adapted from references 1 and 4.

**TABLE 2** Risk Factors for Osteoporosis in Postmenopausal Women*

- Caucasian or Asian heritage
- Premature menopause
- Family history of osteoporosis
- Thin build
- Malnutrition
- Physical inactivity or immobility
- Nulliparity
- Gastric or small bowel resection
- Glucocorticoid therapy
- Heparin therapy
- Hyperparathyroidism
- Smoking
- Excessive alcohol use

* Adapted from references 6 and 7.
Biochemical markers of bone turnover (i.e., the rate of resorption and formation) in serum and urine (Table 3) are not used for diagnosis. However, they may be useful for assessing the response and adherence to treatment. The most commonly used marker in the United States is urinary and serum collagen type I cross-linked N-telopeptide, a marker of bone resorption.

The laboratory work-up for a patient with a diagnosis of osteoporosis includes a variety of assays to exclude secondary causes of the disease. These assays include thyroid function tests, serum calcium, 24-hour urinary calcium excretion, serum or urine protein electrophoresis to exclude multiple myeloma, and serum concentrations of calcium, phosphorus, alkaline phosphatase, parathyroid hormone, 25-hydroxycholecalciferol (a vitamin D precursor), and 1,25-dihydroxycholecalciferol (the active form of vitamin D). Free testosterone is often measured in men to check for hypogonadism.

### Nonprescription Interventions

Various nonprescription drug and nonpharmacologic interventions may be used to prevent and treat postmenopausal osteoporosis. Some of the risk factors for osteoporosis in postmenopausal women are modifiable with lifestyle modification (e.g., exercise, smoking cessation, reducing consumption of caffeine and alcohol). Efforts to improve lighting and remove physical hazards in the home that can cause falls and the use of undergarments with hip protectors are recommended for individuals with osteoporosis who are at risk for falls and fractures.

Ensuring adequate calcium and vitamin D intake is the cornerstone of any regimen to prevent or treat postmenopausal osteoporosis. Bone mass increases during the first 3 decades of life, reaching a peak at around the age of 30. Ensuring an adequate calcium and vitamin D intake at an early age can optimize the peak bone mass and reduce the risk for postmenopausal osteoporosis.

### Calcium

Epidemiologic studies have shown that calcium supplementation increases BMD and is linked to decreased risk for vertebral and hip fractures. Results from a recently completed 5-year, randomized controlled trial showed that supplementation with calcium carbonate 1,200 mg/day decreased clinical fractures in subjects who were compliant with their medications compared with placebo (10.2% vs. 15.4%; hazard ratio, 0.66; 95% confidence interval [CI], 0.45-0.97). The National Academy of Sciences dietary reference intakes for calcium (1,000-1,500 mg/day) than the National Academy of Sciences dietary reference intakes for older Americans.

Diet is a good source of calcium (Table 5). However, many patients (especially the elderly and patients with lactose intolerance) have difficulty consuming enough food to obtain adequate amounts of calcium. Moreover, dietary sources of calcium may provide excessive amounts of calories, fat, or both. Oral calcium supplements are recommended for patients who are
unable to obtain adequate amounts of calcium from the diet.\textsuperscript{7} Most oral calcium supplements should be taken with meals to optimize absorption, which requires an acidic environment (calcium citrate is an exception because it does not need an acidic environment for absorption and may be taken without food).\textsuperscript{3,19} The gut cannot absorb calcium doses greater than 600 mg; thus, calcium supplements should be taken in divided doses.\textsuperscript{3} The elemental calcium content and cost of various calcium supplements vary. Calcium carbonate, which contains about 400 mg (40%) elemental calcium per gram of calcium carbonate, is preferred because it is the least expensive salt and requires the least number of tablets to reach dietary goals.\textsuperscript{3} Because calcium carbonate requires an acidic environment for absorption, it may not be suitable for individuals who receive proton pump inhibitors or histamine H\textsubscript{2}-receptor antagonists.\textsuperscript{3} Although it is more costly, calcium citrate may be used instead because absorption of calcium from this salt does not depend on the presence of acid.\textsuperscript{3} It contains about 21% elemental calcium.\textsuperscript{3} Adequate vitamin D is required for calcium absorption from all calcium salts.

**Vitamin D**

Exposure of the skin to ultraviolet light leads to the formation of cholecalciferol (vitamin D3). Cholecalciferol is converted to 25-hydroxycholecalciferol in the liver and then to the active form, 1,25-dihydroxycholecalciferol, in the kidneys. The active form of vitamin D plays a vital role in promoting intestinal calcium absorption. Parathyroid hormone activates vitamin D in the kidneys in response to low calcium concentrations. Excessive calcium concentrations inhibit parathyroid hormone through a negative feedback mechanism.

Age-related vitamin D deficiency is common because of limited exposure to ultraviolet light (especially in northern latitudes in the United States). In addition, advanced age is associated with diminished renal and hepatic conversion of vitamin D precursors, decreased renal response to parathyroid hormone, and increased resistance of intestinal mucosal cells to the active form of vitamin D.\textsuperscript{19}

The National Academy of Sciences dietary reference intakes for vitamin D, are listed in Table 4. Although these figures reflect an increase in needs in older persons (aged 51 years and older), they are inadequate to meet requirements. Many clinicians recommend 800-1,000 units/day.\textsuperscript{3}

Serum 25-hydroxycholecalciferol levels of 30-60 ng/mL are considered optimal.\textsuperscript{20,21} Levels less than 30 ng/mL are insufficient, and concentrations less than 20 ng/mL are deficient. Levels of 60-90 ng/mL are high and those above 90 ng/mL are toxic. Diet (e.g., fatty fish, eggs) is a source of cholecalciferol and ergocalciferol (vitamin D2, which is obtained from plant sources and metabolized in the body in a manner similar to vitamin D3), although the diet is not a particularly good source. Milk and certain other foods (e.g., orange juice, breakfast cereals) are often fortified with cholecalciferol or ergocalciferol in the United States. Nevertheless, dietary vitamin D intake often is inadequate and supplementation is needed, especially for older Americans. Increasing skin exposure to ultraviolet light is not advised because of the risk of skin cancer. Furthermore, sunscreen prevents the necessary ultraviolet wave lengths from converting skin cholecalciferol to vitamin D. Cod liver oil is a source of vitamin D but it also contains vitamin A, which is associated with bone toxicity.\textsuperscript{3}

Vitamin D supplementation alone does not appear to reduce the incidence of hip or vertebral fractures, but use of vitamin D in combination with calcium has been shown to be effective in reducing the risk of vertebral and nonvertebral fractures, including hip fractures.\textsuperscript{22} In a randomized, placebo-controlled study of 3,270 healthy, elderly ambulatory women who were followed for 18 months, 1,200 mg/day of elemental calcium and 800 units/day of cholecalciferol provided a 43% reduction in the number of hip fractures (P = 0.043) and a 32% reduction in the number of nonvertebral fractures (P = 0.015).\textsuperscript{23} A reduction in nonvertebral fractures was observed over a 3-year period from the use of calcium 500 mg/day and vitamin D 700 units/day in a randomized, placebo-controlled study of 389 elderly, noninstitutionalized men and women.\textsuperscript{24} Of the 37 subjects who had nonvertebral fractures, 26 were in the placebo group and 11 were in the calcium plus vitamin D group (P = 0.02). Recently published data from the Women’s Health Initiative, a randomized, placebo-controlled study in 36,282 healthy, postmenopausal women aged 50 to 79 years, demonstrated that the use of elemental calcium 1,000 mg/day and vitamin D3 400 units/day over an average of 7 years resulted in a 1.06% increase in hip BMD compared with the placebo group (P < 0.01). Calcium plus vitamin D3 supplementation did not significantly reduce the incidence of hip

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**Table 5. Examples of Dietary Sources of Calcium***

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving Size</th>
<th>Amount of Elemental Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yogurt (plain, low-fat)</td>
<td>8 oz</td>
<td>415</td>
</tr>
<tr>
<td>Ricotta cheese (part skim milk)</td>
<td>1/2 cup</td>
<td>335</td>
</tr>
<tr>
<td>Skim or fat-free milk</td>
<td>1 cup</td>
<td>306</td>
</tr>
<tr>
<td>Swiss cheese</td>
<td>1 oz</td>
<td>224</td>
</tr>
<tr>
<td>Fortified orange juice</td>
<td>1 cup</td>
<td>350</td>
</tr>
<tr>
<td>Provolone cheese</td>
<td>1 oz</td>
<td>214</td>
</tr>
<tr>
<td>Cheddar cheese</td>
<td>1 oz</td>
<td>204</td>
</tr>
<tr>
<td>Salmon (canned with bones)</td>
<td>3 oz</td>
<td>181</td>
</tr>
<tr>
<td>American cheese food (pasteurized processed)</td>
<td>1 oz</td>
<td>162</td>
</tr>
<tr>
<td>Low-fat (1%) cottage cheese</td>
<td>1 cup</td>
<td>138</td>
</tr>
<tr>
<td>Macaroni and cheese (canned)</td>
<td>1 cup</td>
<td>88</td>
</tr>
<tr>
<td>Almonds</td>
<td>1/2 cup</td>
<td>200</td>
</tr>
<tr>
<td>Tofu</td>
<td>1/3 cup</td>
<td>150</td>
</tr>
</tbody>
</table>

* Adapted from reference 18.
fractures, and it increased the risk of kidney stones. However, when the analysis was limited to adherent patients, the reduction in risk for hip fracture was significant.25

Vitamin D supplementation appears to reduce the risk of falls in ambulatory older individuals.26 Data from 5 randomized controlled trials involving 1,237 subjects showed that vitamin D reduced the corrected odds ratio (OR) of falling by 22% (corrected OR, 0.78; 95% CI, 0.64-0.92).26 Research in elderly patients with a history of falls suggests that the reduction in falls associated with vitamin D supplementation might be mediated by improvements in neuromuscular function.27

Serum half-life for vitamin D supplements is long and weekly doses may suffice, although daily administration in combination with calcium is convenient.7 A combination product containing the osteoporosis drug alendronate and cholecalciferol 2,800 units that is taken weekly was recently introduced. Vitamin D supplements include cholecalciferol and ergocalciferol. Cholecalciferol is often preferred because it has greater potency than vitamin D2. In addition, intake recommendations for vitamin D are based on vitamin D3 not D2, which makes it easier with vitamin D3 to decide what dose to take. Calcitriol is the active form of vitamin D (i.e., 1,25-dihydroxycholecalciferol). Calcitriol may stimulate bone formation by osteoblasts, but it has a narrow therapeutic index.28,29 Calcitriol is a prescription medication and is often reserved for patients with renal impairment who cannot create the active moiety. Alfacalcidol is a safer analogue that recently became available as a prescription medication in the United States.30

Exercise

Prolonged physical inactivity results in bone loss.11 Weight-bearing (e.g., walking a mile) and resistance exercises are recommended for postmenopausal women because they help preserve BMD.3 Exercise reduces the risk of falls in the elderly by improving strength, balance, and coordination.7,31

Smoking Cessation

Smoking cessation should be advocated for patients with or at risk for postmenopausal osteoporosis.7 Cigarette smoking reduces BMD, increases estrogen metabolism, and leads to early menopause and malnutrition in addition to causing harm to the lungs.3,31

Caffeine

Caffeine has a diuretic effect that leads to the loss of calcium in the urine when 2 to 5 cups of caffeinated beverages are consumed daily.5 Therefore, limiting caffeine intake and increasing consumption of calcium-rich beverages, foods, or supplements (e.g., fat-free or skim milk) can be beneficial for postmenopausal women.5

Alcohol

Postmenopausal women should be advised to limit their weekly intake of alcoholic beverages to 7 drinks.7 One 12-ounce beer, 4 ounces of wine, or 1 ounces of liquor is considered 1 drink.7 Excessive alcohol consumption causes liver toxicity, has a diuretic effect that can lead to calcium loss, and has been linked with low BMD, falls, and fractures.7

Conclusion

Postmenopausal osteoporosis is the result of estrogen deficiency and excessive bone resorption. Lifestyle changes to address modifiable risk factors for the disease, particularly ensuring an adequate calcium and vitamin D intake, are beneficial for the prevention and treatment of the disease.

DISCLOSURES

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Prescription Drug Therapies for Prevention and Treatment of Postmenopausal Osteoporosis

MARY BETH O'CONNELL, PharmD, BCPS, FASHP, FCCP

ABSTRACT

OBJECTIVE: To characterize the changes in bone mass with age in men and women, explain the physiology and pathophysiology of the bone remodeling process, identify the targets for prescription osteoporosis drugs in this process, and provide details about the uses, efficacy, safety, and economics of prescription drug therapies for osteoporosis prevention and treatment.

BACKGROUND: Preventing accelerated bone loss and decreasing age-related decreases in bone density are the primary goals of prescription drug therapy for osteoporosis. Bisphosphonates are the drugs of choice for preventing and treating postmenopausal osteoporosis. Alternatives for patients who cannot take bisphosphonates include raloxifene and calcitonin salmon.

SUMMARY: Menopause is accompanied by a rapid loss in bone mass that is followed by annual losses due to aging in women, which are similar to age-related bone mass decreases in men. Most prescription drug therapies for osteoporosis prevention or treatment reduce bone resorption by inhibiting osteoclast activation and activity, with only one medication class able to increase bone formation by stimulating bone formation by osteoblasts. Denosumab, an investigational monoclonal antibody that inhibits nuclear factor κB ligand, would be a new class of antiresorptive medications. Bisphosphonates currently are the drugs of choice for preventing and treating osteoporosis, with 7- and 10-year safety data available for risedronate and alendronate, respectively. Weekly and monthly regimens of bisphosphonates improve patient acceptance. Recently, an injectable form of ibandronate received U.S. Food and Drug Administration approval for once every 3 months administration. Raloxifene and calcitonin salmon are alternatives for patients who cannot take bisphosphonates because of contraindications or adverse effects. Teriparatide, a recombinant parathyroid hormone fragment, not only increases bone mineral density but also increases bone connectivity.

CONCLUSIONS: Osteoporosis medications are usually safe, especially if used correctly with proper patient education. Treating osteopenia has not been found to be cost effective in women. However, obtaining a dual-energy X-ray absorptiometry scan and treating osteoporosis has resulted in cost savings in senior women living in community and nursing home residences. Pharmacists have multiple opportunities for preventing and treating osteoporosis.

KEYWORDS: Bisphosphonates, Calcitonin salmon, Bone remodeling, Postmenopausal osteoporosis, Raloxifene, Teriparatide


PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS

Prevention of postmenopausal osteoporosis should begin during childhood because bone mass increases during the first 3 decades of life, reaching a peak at around the age of 30 years. Men achieve a higher peak bone mass than women. A slow loss of bone mass begins in both sexes when a person is in her or his mid-30s (Figure 1). A rapid loss of bone mass occurs after menopause in women because of estrogen deficiency. Women experience a loss of 10% to 25% of bone mass in the decade after menopause. Age-related bone loss begins 10 to 15 years after menopause in women and at about the age of 55 years in men. Age-related bone loss occurs at a similar rate in women and men.

The goals of interventions to prevent and treat osteoporosis depend on a patient's life stage (i.e., age) and gender. In both sexes, maximizing peak bone mass is sought during childhood and adolescence, and preserving bone mass by avoiding bone loss is the goal in adulthood in men and from young adulthood until menopause in women. During menopause and the early postmenopausal period, efforts are directed toward preventing the accelerated bone loss that typically occurs during this period. Prevention of further bone loss is the goal in men after the age of 55 years and from late postmenopausal period thereafter in women. In senior citizens of both sexes, prevention of falls and fractures is an additional key goal, especially in persons with a low bone mass.

Bone Physiology and Pathophysiology

Bone is a dynamic organ, with bone resorption by osteoclasts, bone formation by osteoblasts, bone mineralization, and quiescence occurring simultaneously. Bone mineralization requires calcium, phosphate, and magnesium, which provide strength and rigidity. Bone remodeling (i.e., resorption and formation) maintains skeletal strength by repairing microscopic damage. It also maintains the serum calcium concentration within the range needed for physiologic functions. Remodeling is regulated by estrogen, receptor activator of nuclear factor κB (RANK) ligand, parathyroid hormone (PTH), calcitonin, vitamin D, prostaglandins, interleukins, growth factors, tissue necrosis factor, bone morphogenic proteins, and various other hormones and cytokines.

The RANK ligand, a cytokine produced by osteoblasts, binds to a receptor on osteoclasts and promotes their differentiation, maturation, and activation. The RANK ligand also decreases apoptosis and increases the life span of osteoclasts. Activated osteoclasts attach to bone by integrins, forming a tight seal. The osteoclast ruffled border secretes hydrogen ions, H+ATPase, and the protease cathepsin K, which dissolve bone. Osteoblasts also produce osteoprogerin to produce a negative feedback loop. Osteoprogerin competes with the RANK ligand for binding at

Author

MARY BETH O'CONNELL, PharmD, BCPS, FASHP, FCCP, is an associate professor, Pharmacy Practice Department, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan.

AUTHOR CORRESPONDENCE: Mary Beth O’Connell, PharmD, BCPS, FASHP, FCCP, Associate Professor, Pharmacy Practice Department, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, 259 Mack Ave., Suite 2190, Detroit, MI 48201-2417. Tel: (313) 577-0824; Fax: (313) 577-5369; E-mail: mbocconnell@wayne.edu

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Receptors on osteoclasts, thereby preventing differentiation of osteoclasts and thus inhibition of bone resorption. Estrogen stimulates osteoblasts and inhibits osteoclasts.

Various conditions, diseases, medications, and aging can perturb normal bone remodeling. Menopause is associated with estrogen deficiency and thus opposing effects to premenopausal estrogen sufficiency. Diseases and medications can have multiple deleterious effects from decreasing gut calcium absorption to accelerating bone loss. Bone loss due to normal aging is a function of inadequate bone formation in addition to other aspects of aging, such as poor diet, comorbid conditions, and medications.

Osteoporosis Medication Pharmacology

Prescription drugs used to prevent or treat postmenopausal osteoporosis act on various parts of the bone remodeling process. They vary by U.S. Food and Drug Administration (FDA) approvals for prevention and/or treatment (Table 1). Since efficacy with osteoporosis medications was generally studied concomitantly with calcium or calcium and vitamin D, these supplements should probably be used in combination with osteoporosis medications.

Bisphosphonates decrease osteoclast function by inhibiting osteoclast formation, recruitment, survival, and adherence to bone. Etidronate, a first-generation bisphosphonate, is rarely used for the prevention or treatment of osteoporosis because the drug is associated with osteomalacia. It is not approved by the FDA for osteoporosis indications. Alendronate, a more potent oral second-generation agent, was the first bisphosphonate approved by the FDA.

Pamidronate, another second-generation injectable bisphosphonate, is not approved by the FDA for the prevention or treatment of osteoporosis. Oral risedronate, oral and injectable ibandronate, and injectable zoledronic acid (investigational for osteoporosis) are third-generation bisphosphonates with greater potency than second-generation agents. The binding affinities of bisphosphonates differ (in descending order from highest to lowest binding affinity, they are zoledronic acid, alendronate, ibandronate, risedronate, and etidronate), with possible implications for drug persistence in bone and longer duration of action.

FIGURE 1: Bone Health Therapeutic Algorithm

BMD = bone mineral density; CBC = complete blood count; DXA = dual-energy X-ray absorptiometry; OH = hydroxy; PTH = parathyroid hormone; TSH = thyroid-stimulating hormone.
Selective estrogen receptor modulators (e.g., raloxifene) act as agonists at estrogen receptors on both osteoblasts and osteoclasts. Calcitonin salmon acts directly on osteoclast receptors to suppress their activity. Denosumab mimics the action of osteoprotegerin by turning off osteoclast activity and is investigational.

Postmenopausal estrogen therapy (ET) appears to directly inhibit osteoclasts and is approved for prevention although with limited use after the Women’s Health Initiative trials.

Although bone resorption is associated with hyperparathyroidism and large doses of parathyroid hormone, smaller doses increase osteoblast differentiation and activity. These latter effects are achieved with teriparatide, a recombinant human parathyroid hormone fragment, and investigational PTH 1-84.

Several investigational agents are being explored to inhibit other aspects of resorption and to enhance other aspects of formation. Investigational osteoporosis drug classes include integrin receptor antagonists, cathepsin K inhibitors, recombinant human insulin-like growth factor 1, H+ATPase inhibitors, interleukin-1 receptors, calcioometrics, and calciolysics. Efforts to develop compounds with the characteristics of osteoprotegerin that bind to the RANK receptor and inhibit osteoclast activation have not been successful because of antibody formation.

### Treatment Algorithm

Bone mineral density (BMD) testing (see the preceding article by Kamel in this supplement) of the spine and hip is appropriate before initiating treatment with prescription osteoporosis medications in women aged 65 years and older, women aged 60 to 64 years who are at increased risk for osteoporotic fractures, and men at increased risk for fractures (Figure 1). Treatment with

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dosage Forms and Recommended Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Prevention of osteoporosis in postmenopausal women</td>
<td>35 mg tablet weekly</td>
</tr>
<tr>
<td></td>
<td>Treatment of osteoporosis in postmenopausal women or to increase bone mass</td>
<td>70 mg tablet weekly</td>
</tr>
<tr>
<td></td>
<td>in men and women</td>
<td>70 mg tablet with 2,800 units vitamin D weekly</td>
</tr>
<tr>
<td></td>
<td>Prevention of osteoporosis in postmenopausal women</td>
<td>70 mg as oral solution weekly</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Prevention and treatment of osteoporosis in postmenopausal women</td>
<td>5 mg tablet daily</td>
</tr>
<tr>
<td></td>
<td>Prevention and treatment of glucocorticoid-induced osteoporosis* in men</td>
<td>5 mg tablet daily†</td>
</tr>
<tr>
<td></td>
<td>and women</td>
<td></td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Prevention of osteoporosis in postmenopausal women</td>
<td>2.5 mg tablet daily</td>
</tr>
<tr>
<td></td>
<td>Treatment of osteoporosis in postmenopausal women</td>
<td>150 mg tablet monthly‡</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Prevention and treatment of postmenopausal osteoporosis</td>
<td>60 mg tablet daily</td>
</tr>
<tr>
<td>Calcitonin salmon</td>
<td>Treatment of osteoporosis in women 5 years postmenopausal</td>
<td>200 units daily alternating nares</td>
</tr>
<tr>
<td>Estrogen or estrogen and progestin therapy</td>
<td>Prevention of postmenopausal women</td>
<td>Various doses and products§</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Treatment of osteoporosis in women and men at high risk for fracture</td>
<td>20 mcg subcutaneous injection daily</td>
</tr>
</tbody>
</table>

* Glucocorticoid-induced osteoporosis is associated with long-term use of the equivalent of prednisone 7.5 mg/day or more.
† A 28-day blister pack is available with four 35-mg risedronate tablets to be taken weekly and twenty-four 1,250 mg calcium carbonate tablets (containing the equivalent of 500 mg elemental calcium) to be taken on days 2-7 of each 7-day treatment period.
‡ Missed doses of 150 mg ibandronate tablets may be taken only if more than 7 days will elapse before the next scheduled dose (two 150 mg tablets should not be taken within 1 week).
§ Minimal use after the Women’s Health Initiative studies; however, small doses for short durations still advocated for menopausal symptom control or in patients who cannot tolerate any of the other osteoporosis medications.

FDA = U.S. Food and Drug Administration; IV = intravenous.
Prescription Drug Therapies for Prevention and Treatment of Postmenopausal Osteoporosis

osteoporosis medications may be considered without first testing for BMD in men and women with a fragility fracture or using systemic glucocorticoids on a long-term basis. A Z-score less than -2.0 (see the preceding article by Kamel et al. in this supplement) suggests the need for a diagnostic work-up to identify a secondary cause of osteoporosis. Drug therapy is not indicated for patients with a normal BMD (a T-score $>1$), and its use is controversial in patients with osteopenia (a T-score between -1 and -2.5) and most likely is not cost effective. BMD testing should be performed every 1 to 5 years in patients with normal BMD or osteopenia. If a patient has spinal osteoporosis (i.e., a spine T-score $<-2.5$), a bisphosphonate, raloxifene, or calcitonin salmon could be tried, in that order. All of these therapies have been shown to decrease vertebral fractures, but only the bisphosphonates have been shown to decrease the incidence of hip fractures. Therefore, if hip osteoporosis is present (i.e., a hip T-score $<-2.5$), treatment with a bisphosphonate is preferred. If the patient is intolerant to oral bisphosphonates, a parenteral bisphosphonate, teriparatide, raloxifene, and calcitonin salmon are alternatives.

**Bisphosphonates**

Bisphosphonates are the drugs of choice for preventing and treating osteoporosis. The drugs increase BMD in a dose-dependent manner, and they produce significant reductions in the risk of hip, spine, and nonvertebral fractures. The efficacy of bisphosphonates has been demonstrated in both women and men, including the elderly. The response to bisphosphonates is greater in patients with a low BMD than in patients with a high BMD. The increase in BMD from bisphosphonates is enhanced by concomitant ET or raloxifene but is inhibited by concomitant PTH/teriparatide therapy. Adequate calcium and vitamin D intake is also needed for the beneficial effects of bisphosphonates to be observed.

Bisphosphonates can irritate the upper gastrointestinal (GI) mucosa, but the drugs are relatively safe if the patient has no serious underlying GI disorders. Bisphosphonates should not be used in patients with esophageal strictures or achalasia or for those who are unable to stand or sit upright for at least 30 minutes (at least 60 minutes for ibandronate) after drug administration.

Bisphosphonates may be used in patients with gastroesophageal reflux disease and patients who take aspirin or nonsteroidal anti-inflammatory drugs. Nausea, abdominal pain, and dyspepsia are the most common adverse effects from bisphosphonates. Esophageal perforation and bleeding are rare. Switching to a formulation that is administered weekly or monthly instead of daily might minimize these effects. The cells that line the GI tract regenerate in about 5 days, with the longer dosing intervals allowing for cellular regeneration between doses.

Osteonecrosis of the jaw has been infrequently reported in patients receiving bisphosphonates (particularly with the injectable agents pamidronate and zoledronic acid), primarily in patients receiving chemotherapy or corticosteroids or in association with tooth extraction, surgery, or infection. Muscle, bone, and joint pain that usually abates after discontinuing the drug and a flu-like syndrome, with fever, chills, flushing, and musculoskeletal pain, also have been reported. Bisphosphonates should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) because of a lack of data.

**Alendronate**

Long-term efficacy and safety data are available from more than 10 years of alendronate use. Progressive increases in spine and hip BMD were observed over a 10-year period in a randomized, double-blind study of 247 postmenopausal women with osteoporosis who received the bisphosphonate alendronate 5 mg/day or 10 mg/day. The greatest increases in BMD were observed during the first 3 to 5 years of treatment and with the 10-mg dose. A tendency to reach a plateau in hip BMD was observed after about 5 years, but progressive increases in spine BMD continued throughout the 10-year period. The 10-year increases in BMD from baseline after 10 mg per day for 10 years was 13.7% for lumbar spine, 10.3% for trochanter, 5.4% for femoral neck, and 6.7% for proximal femur.

The increased BMD from bisphosphonate therapy is maintained or slightly diminished after discontinuation of the drug but is better than placebo therapy. The effects on spine and hip BMD from alendronate 2.5 to 20 mg daily for 2, 4, or 6 years followed by no treatment for 7, 5, or 3 years, respectively, were evaluated in a placebo-controlled study of 203 postmenopausal women. The rate of bone loss after all doses of alendronate discontinuation was comparable to the rate observed with placebo, thus due to normal aging, not related to a drug-induced accelerated rate of bone loss such that is seen with ET discontinuation. A benefit from alendronate over placebo was observed for up to 7 years after discontinuation of the drug. This study provides valuable information about duration of therapy, but no there is no consensus yet on how long to continue bisphosphonate therapy or at what point to reintivate therapy.

**Risedronate**

Clinical trials have also documented long-term (up to 5 years) BMD efficacy and safety with risedronate. In a 1-year randomized, double-blind study of 1,053 women with postmenopausal osteoporosis (Fosamax Actonel Comparison Trial [FACT]), the efficacy of once-weekly risedronate (35 mg) and once-weekly alendronate (70 mg) in increasing BMD was compared. Significantly greater increases in BMD were observed with alendronate than with risedronate. The differences measured in the BMD were 1.4% for hip trochanter (P <0.001), 1.0% for total hip (P <0.001), 0.7% for femoral neck (P <0.01), and 1.2% for lumbar spine (P <0.001). However, the clinical significance of these findings cannot be extrapolated to a difference in the impact of the drugs on fractures. This study most likely will never be
conducted because of the large number of patients required. With the evolving science of bone remodeling and osteoporosis, a medication's impact on bone structure will most likely become more important than BMD changes only.

In a 2-week study of 515 healthy, postmenopausal women, risedronate 5 mg/day was associated with a significantly lower risk of gastric ulcers than alendronate 10 mg/day, 4.1% versus 13.2%, respectively (P <0.001), potentially because of differences in the GI damage from pyridinyl bisphosphonates (e.g., risedronate) and amino bisphosphonates (e.g., alendronate). Comparative studies over a longer duration and with weekly therapy are needed to determine whether the risk of upper GI adverse effects from these bisphosphonates differs clinically.

Ibandronate

Ibandronate is the newest bisphosphonate to reach the market. It is unique among bisphosphonates because it may be given orally on a monthly or daily basis or as a quarterly injection. Potential advantages of an injectable bisphosphonate formulation include a lower risk of GI adverse effects because of less irritation of the GI mucosa and improved bioavailability and patient adherence. Although the use of the injectable route of administration is not as convenient and is more costly than the oral route, it might be preferred in patients in a long-term-care setting who cannot remain sitting or standing for at least 30 to 60 minutes after drug administration or in patients with GI diseases in whom oral therapy is contraindicated.

The efficacy of oral ibandronate 2.5 mg/day with calcium 500 mg and vitamin D 400 units in reducing the risk of fractures was demonstrated in a pivotal, 3-year, randomized, double-blind, placebo-controlled, parallel-group study of 2,946 postmenopausal women with osteoporosis. Ibandronate produced significantly greater increases from baseline in lumbar spine (6.5% vs. 1.3%, respectively; P <0.0001) and hip BMD (3.4% vs. -0.7%, respectively; P <0.0001) than placebo. The rate of new vertebral fractures was 4.7% with ibandronate and 9.6% with placebo, representing a 62% reduction (P = 0.0001) in fractures with the bisphosphonate treatment. Ibandronate produced a significant 49% reduction (P = 0.0117) in clinical vertebral fractures (i.e., fractures confirmed by X-ray and accompanied by pain), representing an absolute difference of 2.5%. The incidence of nonvertebral fractures was similar with ibandronate (9.1%) and placebo (8.2%). However, in a post hoc analysis of a subset of high-risk patients with a particularly low femoral neck BMD (T-score <-3.0), ibandronate therapy was associated with a significantly lower incidence of nonvertebral fractures than placebo (about 7.5% vs. 14.8%, respectively; 69% relative risk reduction, P = 0.013). The incidence of adverse drug reactions was similar with ibandronate (20%) and placebo (18%).

The efficacy of using a monthly dose of ibandronate instead of a daily dose for treating postmenopausal osteoporosis was demonstrated in a 2-year, randomized, double-blind, phase 3, noninferiority trial known as the Monthly Oral Ibandronate in Ladies (MOBILE) study. Several monthly doses (100 mg as 2 divided doses on 2 consecutive days, 100 mg on a single day and 150 mg on a single day) were compared with 2.5 mg/day in 1,609 women with postmenopausal osteoporosis. The women also took supplements (calcium 500 mg and vitamin D 400 units) daily. After 1 year of treatment, all of the monthly ibandronate doses were judged noninferior to the daily dose for increasing lumbar spine, hip, femoral neck, and trochanter BMD, with the greatest increases from baseline in the monthly 150-mg dose group. The incidence of adverse effects leading to withdrawal from the study was similar with monthly drug administration (5.1%-6.3%) and daily therapy (7.3%).

Ibandronate 3 mg intravenous (IV) every 3 months and 2.5 mg/day orally were compared in a double-blind, double-dummy, phase 3 study of 1,395 women with postmenopausal osteoporosis (Dosing Intravenous Administration [DIVA] study). Calcium (500 mg/day) and vitamin D (400 units/day) supplements were provided to all women. After 1 year of treatment, significantly greater increases from baseline in lumbar spine BMD were associated with IV therapy (4.8%) than with oral therapy (3.8%; P <0.001). Increases in total hip, femoral neck, and trochanter BMD also were greater with IV therapy than oral therapy.

Patient preferences for weekly alendronate 70-mg doses or monthly ibandronate 150-mg doses were evaluated in a 6-month, prospective, randomized, open-label study of 342 women with postmenopausal osteoporosis (Boniva Alendronate Trial in Osteoporosis [BALTO] study). A 2-period, 2-sequence crossover treatment design was used. Significantly more women (66%) preferred monthly ibandronate therapy than weekly alendronate therapy (27%; P <0.0001). Seven percent of participants had no preference for either drug or dosing frequency. Greater tolerability of adverse effects was a reason for 17% of patients who preferred monthly ibandronate and 4% of patients who preferred weekly alendronate. The incidence of adverse effects was similar, with approximately 12% of both groups reporting GI adverse effects.

Zoledronic Acid

Zoledronic acid (zoledronate), a potent, third-generation injectable bisphosphonate, is currently approved by the FDA for bone metastasis and malignant hypercalcemia and investigational for the prevention or treatment of osteoporosis. The effects of 5 different IV zoledronic acid regimens on BMD were evaluated in a 1-year, randomized, double-blind, placebo-controlled study of 351 postmenopausal women with low BMD. Zoledronic acid 0.25 mg, 0.5 mg, or 1 mg or placebo were given at 3-month intervals. A fifth group received a single 4-mg dose, and the sixth group received two 2-mg doses 6 months apart. All 5 zoledronic acid regimens produced significantly greater but somewhat similar BMD increases from baseline compared with the mean placebo group response in lumbar spine (4.3 to 5.1% greater response, P <0.001) and femoral neck BMD (3.1 to 2.5% greater response,
P <0.001). All zoledronic acid regimens suppressed biochemical markers of bone resorption to a significantly greater extent than placebo throughout the study. The incidence of myalgia and pyrexia was higher in the zoledronic acid groups than in the placebo group. Treatment-related side effects were 45% to 67% in the zoledronic acid groups versus 27% in the placebo group (P <0.05); however, the treatment-related dropout rates for zoledronic acid (3% to 7%) were similar to the placebo group (2%).

### Patient Education

Patient education is vital for the safe and effective use of bisphosphonates to prevent and treat osteoporosis. The bioavailability of oral bisphosphonates is low, and food and beverages other than plain water can further reduce bioavailability. Therefore, patients should be advised to take the medication at least 30 minutes before the first food or beverage (other than plain water) of the day, and take the medication only with a full (6-8 oz.) glass of plain water (not mineral water, orange juice, coffee, sodas, or milk). Patients also should be advised not to lie down for at least 30 minutes (60 minutes for ibandronate) after taking the medication to facilitate delivery to the stomach and reduce the risk for esophageal irritation. Calcium and other multivalent cations, including antacids, calcium supplements, and multivitamins, should be taken at least 60 minutes after the bisphosphonate because the cations may interfere with bisphosphonate absorption. Patients also should be warned to report difficult or painful swallowing or heartburn to their health care provider. Patient counseling should be ongoing and adherence to therapy should be assessed often. To improve adherence with the once-monthly ibandronate regimen, patients have the option of receiving reminders by regular or electronic mail from the manufacturer (www.myboniva.com).

Although a 30-minute fast is recommended, longer fasts could increase bisphosphonate absorption, according to an alendronate pharmacokinetic study and a recent ibandronate study. The impact on efficacy of changing the duration of fasting after administration of oral ibandronate 2.5 mg/day from 60 minutes to 30 minutes was evaluated in a 48-week, multicenter, open-label, randomized, parallel-group, noninferiority study of 184 women with postmenopausal osteoporosis. The relative increase from baseline in lumbar spine BMD was lower in the 30-minute fast group (3%) than that in the 60-minute fast group (5%). The increase in total hip BMD also was lower with the 30-minute fast than with the 60-minute fast (2% vs. 3%, respectively). Thus, a 30-minute fast did not meet the criteria for noninferiority to a 60-minute fast, so a 60-minute fast is recommended after oral administration of ibandronate.

Ibandronate injection should be administered by health care professionals who have been educated regarding the unique requirements for handling and administering the medication. Ibandronate injection is provided in a kit with a single-use, prefilled, glass syringe containing 3 mg/3 mL of the drug, with a 23-gauge, 1-inch needle and an alcohol wipe. The kits should be stored at controlled room temperature (59°F-86°F). Reconstitution and refrigeration of the drug are not required. The drug should not be mixed with calcium-containing solutions or other IV medications. Ibandronate injection is administered by rapid IV injection over 15 to 30 seconds, using caution not to give it intra-arterially. Treatment with IV bisphosphonates has been associated with renal toxicity, with a risk that appears to be inversely related to the rate of drug administration. The rapid injection of ibandronate over 15 to 30 seconds was not associated with acute renal failure in controlled clinical trials.

### Raloxifene

Raloxifene is currently the only selective estrogen receptor modulator (SERM) approved by the FDA for the prevention and treatment of osteoporosis in postmenopausal women. Positive clinical osteoporosis trial data exist for another SERM, tamoxifen; however, it is only approved by the FDA for the prevention of breast cancer. Other SERMs are in development.

Raloxifene acts as an estrogen agonist in bone and on lipids and as an estrogen antagonist in breast and uterine tissues. Raloxifene increases spine and hip BMD, but not to the same extent as bisphosphonates or ET. Raloxifene reduces the risk of vertebral fractures by 30% to 50% in women with postmenopausal osteoporosis, but it does not affect the rate of nonvertebral fractures. Adding raloxifene to alendronate does not produce greater increases in BMD than using alendronate alone; however, combination therapy is better than raloxifene alone. Whether changes in BMD predict an impact on fractures from raloxifene therapy is not clear since fracture prevention does not correlate with BMD changes for this medication.

To determine if raloxifene had a cardiovascular effect and could add additional benefit during osteoporosis therapy, its effects on lipids and cardiovascular disease and mortality have been evaluated. Decreases in total and low-density lipoprotein cholesterol concentrations with little change in high-density lipoprotein cholesterol and triglyceride concentrations are associated with raloxifene therapy, which are lower than those achieved with ET/hormone therapy (HT). Unlike ET, raloxifene is not associated with negative cardiovascular events. A secondary analysis of cardiovascular event data (i.e., coronary and cerebrovascular events, including myocardial infarction, unstable angina, coronary ischemia, stroke, and transient ischemic attack) from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial revealed that raloxifene treatment over a 4-year period did not significantly affect the risk of cardiovascular events. However, in a subset of women who were at increased risk for cardiovascular events because of the presence of multiple cardiovascular risk factors, a history of coronary events, or a prior revascularization procedure, raloxifene significantly reduced the risk of cardiovascular events compared with placebo. Preliminary data from the Raloxifene Use for The Heart trial (RUTH) found no increases or
decreases in heart disease or mortality with raloxifene (newsroom.lilly.com/ReleaseDetail.cfm?ReleaseID=192692).

Raloxifene's role in osteoporosis therapy could change, at least for a subset of women with or at risk for breast cancer, if it were to receive an FDA approval for breast cancer prevention. The effect of raloxifene on the risk for breast cancer was evaluated in the MORE study. In this randomized, double-blind trial, 7,705 women with postmenopausal osteoporosis received raloxifene 120 mg/day or 60 mg/day or placebo and were followed for a median of 40 months. Raloxifene significantly reduced the incidence of invasive breast cancer by 76%, with 126 the number of women needed to treat 1 case of breast cancer (relative risk reduction changed from 4.3 on placebo to 1.5 with raloxifene). Raloxifene did not increase the risk of endometrial cancer; it increased the risk of venous thromboembolic disease 3-fold, but the incidence was still low (18 cases in 2,557 women).

Raloxifene 60 mg is taken orally once daily. The drug causes hot flushes in as many as 1 in 4 women. Raloxifene is associated with an increased risk of thromboembolism (e.g., deep vein thrombosis), although the incidence is low and it is contraindicated in women with a history of venous thrombosis.

■ Hormone Therapy

HT (estrogen plus a progestin or, for women without a uterus, estrogen alone [ET]) increases BMD in women with or at risk for postmenopausal osteoporosis. A reduced risk for vertebral and hip fractures has been reported in postmenopausal women receiving estrogen plus a progestin, and a reduced risk of hip fractures has been observed in postmenopausal women who received estrogen alone. However, the use of HT to prevent and treat osteoporosis has fallen out of favor because of the findings from the Women's Health Initiative and other research suggesting an increased risk of stroke and cardiovascular disease early in the course of therapy in patients receiving HT or ET. The risks outweigh the benefits of ET or HT in most women, although ET or HT is still approved by the FDA for the prevention (not treatment) of postmenopausal osteoporosis in women who are at significant risk and for whom nonestrogen medications are not appropriate. HT is still advocated for short-term use to manage vasomotor and urogenital symptoms associated with menopause. The lowest effective dose should be used.

■ Calcitonin Salmon

Calcitonin is a natural polypeptide hormone secreted by the thyroid gland in response to high serum calcium concentrations. It decreases bone resorption. Calcitonin salmon is a synthetic form with the same amino acid sequence as that of calcitonin of salmon origin. Calcitonin salmon is approved for the treatment (but not prevention) of postmenopausal osteoporosis in women who are more than 5 years beyond menopause and have a low bone mass. The drug is available as an injection for subcutaneous (SC) or intramuscular administration and a nasal spray. The injectable form is seldom used because it can cause nausea and facial flushing and the nasal spray is better tolerated.

Calcitonin salmon nasal spray 200 units/day decreased the risk of new vertebral fractures by about one third (18% vs. 26%, respectively; P = 0.03) in a large, 5-year study of postmenopausal women with osteoporosis. Of note, the withdrawal rate in this study was 59%. However, the drug does not appear to decrease the risk of hip fractures. There is evidence of a plateau in the effect of calcitonin salmon on markers of bone resorption after 8 weeks of treatment, suggesting that intermittent administration may be appropriate. Further study is needed.

An analgesic effect from intranasal calcitonin salmon has been reported in patients with osteoporotic vertebral fractures. The time to onset of analgesia is as little as 1 week. Analgesia might be the result of endorphin release, an anti-inflammatory effect due to decreased prostaglandin synthesis, direct calcitonin receptor stimulation, or decreased osteoclastic activity. The analgesic effect from calcitonin salmon may reduce the requirements for analgesic medications.

Rhinitis and epistaxis are the most common adverse effects from calcitonin salmon nasal spray. The spray is given as a single daily 200-unit dose. Patients should be instructed to alternate nares daily.

Unopened bottles of calcitonin salmon nasal spray should be stored in the refrigerator, but the bottle in use may be stored at room temperature for up to 35 days. Patients should be instructed how to prime the pump before the first dose, but priming is not required for subsequent doses.

■ Teriparatide

Teriparatide (recombinant human PTH) contains the first 34 amino acids of the 84 amino acids in human PTH. It is administered as a single daily dose by SC injection into the thigh or abdominal wall. A recombinant human PTH product with all 84 amino acids might be approved by the FDA for the treatment of postmenopausal osteoporosis in the near future. Administration of this product by the SC route also appears to increase BMD and reduce the risk of vertebral fractures.

At therapeutic doses, teriparatide increases bone formation by stimulating osteoblast replication and inhibiting osteoblast apoptosis. Teriparatide increases the thickness of outer cortical bone and increases the connectivity of trabecular bone (the interior porous bone found in vertebrae and other bones). These changes increase bone strength and make teriparatide unique among osteoporosis therapies. Although bisphosphonates increase BMD, they do not affect connectivity or strength. Increases in lumbar spine BMD of 9.7% (P <0.001) and femoral neck of 2.8% (P ≤0.001) were significantly greater than placebo. Teriparatide significantly reduced the risk of new vertebral (5% vs. 14%, respectively; relative risk 0.35; 95% confidence interval [CI], 0.22-0.55) and nonvertebral fragility fractures (3% vs. 6%, respectively; relative risk 0.47; 95% CI, 0.25-0.88) compared with placebo in postmenopausal women with osteoporosis.
Teriparatide may be used in conjunction with raloxifene or HT. However, teriparatide should not be used in combination with bisphosphonates because they may reduce the effects of teriparatide.\textsuperscript{36,37} Bisphosphonates can be used before or after PTH therapy, with potentially better results in bisphosphonate-naive patients receiving the bisphosphonate after PTH therapy.

Teriparatide can cause orthostatic hypotension, so patients should be advised to position themselves so that they can sit or lie down if they feel lightheaded after drug administration. Such reactions usually resolve within a few minutes to a few hours and do not preclude continued use of the drug.\textsuperscript{35} Large doses of teriparatide were associated with an increased incidence of osteosarcoma in animal studies, but the relevance of these findings for humans are questionable. Osteosarcoma has not been observed in humans in phase 4 postmarketing surveillance. Teriparatide should not be used for more than 2 years because the safety and efficacy of the drug for periods longer than 2 years have not been evaluated.\textsuperscript{35}

Patient counseling should address the proper storage and administration of teriparatide. The drug is a clear, colorless, 250-mcg/mL solution provided in prefilled pens containing twenty-eight 20-mcg doses. Teriparatide may be self-administered by the patient or a caregiver once she or he receives instructions on proper priming and use of the pen. The drug should be stored under refrigeration (36°F -46°F) and administered without allowing it to warm to room temperature.\textsuperscript{35} The pen should be recapped between uses. Missed doses should be administered as soon as they are remembered, but no more than 1 injection should be administered on the same day.\textsuperscript{31}

\section*{Denosumab}

Denosumab (formerly known as AMG 162) is a humanized monoclonal antibody specific for the RANK ligand. It inhibits osteoclast activation and activity.\textsuperscript{38} The efficacy and safety of denosumab were evaluated in a 12-month, phase 2, randomized, controlled trial of 412 postmenopausal women with low BMD.\textsuperscript{39} Subjects were randomly assigned to receive denosumab 6 mg, 14 mg, or 30 mg SC every 3 months; denosumab 14 mg, 60 mg, 100 mg, or 210 mg SC every 6 months; open-label alendronate 70 mg orally once weekly; or placebo. All patients received calcium and vitamin D supplementation. Denosumab produced increases in lumbar spine (3.0%-6.7%), total hip (1.9%-3.6%), and distal radius (0.4%-1.3%) BMD that exceeded those produced by placebo (P <0.001) and were comparable to or greater than those produced by alendronate (4.6%, 2.1%, -0.5%, respectively). However, small increases in risk for neoplasm (1.9%) and infection (1.0%) were associated with denosumab treatment compared with alendronate (0% for both) or placebo (0% for both). Additional denosumab safety data are needed. Phase 3 clinical trials of denosumab in postmenopausal women with osteoporosis began in 2004.

\begin{table}[h]
\centering
\caption{Incremental Cost-Effectiveness Ratio ($)}
\scriptsize
\begin{tabular}{|l|llll|}
\hline
Age (Years) & -1.5 & -2.0 & -2.4 & <-2.5 \\
\hline
55 & 256,000 & 94,000 & 74,000 & NE \\
65 & 284,000 & 92,000 & 71,000 & 40,100 \\
75 & 332,000 & 109,000 & 86,000 & Cost savings \\
85 & NE & NE & NE & Cost savings \\
95 & NE & NE & NE & Cost savings \\
\hline
\end{tabular}
\end{table}
* Dollar figures represent the cost per quality-adjusted life-year gained by using alendronate instead of no treatment. Values below $50,000 per year are usually considered acceptable in the United States.

\section*{Economics}

Prescription osteoporosis drug therapies (e.g., bisphosphonates, raloxifene, calcitonin salmon, teriparatide) are more costly than nonprescription calcium and vitamin D supplements, most of which cost $5 to $15 per month. The monthly cost of prescription osteoporosis drugs ranges from a low of about $85 for oral bisphosphonates to a high of around $700 for teriparatide. The monthly costs of raloxifene and calcitonin salmon are slightly higher than the oral bisphosphonates. The cost of ibandronate injection is higher than that of oral bisphosphonates, including oral ibandronate, but the greater tolerability might justify the added expense. The high cost of teriparatide might be justified because it is the only osteoporosis drug that increases bone formation and connectivity. Depending on the Medicare Part D plan, usually alendronate or risendronate are covered with varying copays per plan for preferred medications since generic agents are not available. Ibandronate is either at equal bisphosphonate coverage or at the nonpreferred or higher tier copay. Raloxifene and calcitonin salmon are covered at the preferred or middle tier copay. Teriparatide is usually listed as nonpreferred or in the highest tier copay, and prior authorization is often required.

A Markov cost-utility analysis of the benefit of alendronate (compared with no treatment) in postmenopausal women with osteopenia (i.e., at risk for osteoporosis, T-score -1.5 to -2.4) was performed from a societal perspective.\textsuperscript{15} Five years of alendronate therapy was assumed because of the plateau in effect on hip BMD after this duration of treatment.\textsuperscript{21} The analysis used fracture data from the Fracture Intervention Trial, a randomized, blinded, placebo-controlled trial of alendronate.\textsuperscript{49} Medicare costs from 2001 and health care utilization data from an Olmsted County, Minnesota, database also were used.

The incremental cost-effectiveness ratio (i.e., cost per quality-adjusted life-year [QALY] gained) for alendronate therapy in postmenopausal women with osteopenia was determined for 3 different...
ages and 3 different femoral neck T-scores (Table 2). The investigators concluded that alendronate therapy is not cost effective in any of these scenarios, assuming a societal willingness to pay $50,000 per QALY. However, the results of the cost-utility analysis changed when the influence of additional risk factors for fracture other than low BMD (e.g., a family history of fractures) was assessed for 65-year-old postmenopausal women with osteopenia and a T-score of -2.0. As the relative risk for fracture (adjusted for BMD) from added risk factors increased, the cost per QALY decreased. Alendronate treatment became cost effective (i.e., the cost per QALY fell below $50,000) for these patients when the relative risk for fractures reached 2.0 or higher (i.e., a 2-fold or greater increase in the relative risk for fracture). The World Health Organization currently is analyzing risk factors for fracture that will facilitate cost-effectiveness analyses and patient selection for therapy in the future.

A similar cost-utility model was developed by the same investigators to evaluate the cost-effectiveness from a societal perspective of universal bone densitometry screening measurements in women aged 65 years or older followed by 5 years of alendronate treatment in those with a femoral neck T-score of -2.5 or lower (i.e., a diagnosis of osteoporosis). The cost per QALY gained by using alendronate instead of no treatment was $43,000 for women aged 65 years and $5,600 for women aged 75 years. In women aged 85 years living in nursing homes, the cost per QALY gained from alendronate therapy was $7,300 to $12,900. Alendronate was cost saving for women aged 85 and 95 years living in the community (i.e., ambulatory) and women aged 95 years living in nursing homes. Thus, universal bone densitometry screening for women aged 65 years or older and the use of alendronate therapy for women with osteoporosis were cost effective.

# Conclusion

Preventing the accelerated bone loss associated with the early postmenopausal period and decreasing aging-related decreases in bone density are the primary goals of prescription osteoporosis drug therapy. Bisphosphonates are the drugs of choice for preventing and treating postmenopausal osteoporosis. Increasing the dosing interval might increase patient acceptance and adherence by improving convenience. Alternatives for patients who cannot take bisphosphonates include raloxifene and calcitonin salmon. Teriparatide is used to build new bone in patients with significant osteoporosis and should not be used concomitantly with a bisphosphonate. The cost-effectiveness of osteoporosis drug therapies depends on patient age, BMD, and other risk factors for the disease; however, treating osteoporosis with a bisphosphonate in senior women is cost effective and using it to prevent preventing osteoporosis in women with osteopenia is not.

## DISCLOSURES

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## REFERENCES


Prescription Drug Therapies for Prevention and Treatment of Postmenopausal Osteoporosis


Medication nonadherence is a major public health problem. Adherence to long-term therapy for chronic illnesses in developed countries averages 50%.1 The rates of adherence in developing countries are even lower.1 In people aged 60 years or older, rates of adherence to medication regimens range from 41% to 74%.2 Many patients have difficulty following treatment regimens.1

The terms compliance, persistence, and adherence often are used interchangeably, but they have distinctly different meanings. Compliance is the consistency and accuracy with which a medication regimen is followed. Persistence is the length of time a regimen is continued. Adherence reflects both compliance and persistence.

Adherence, in general, results from an intricate and complex interaction among an individual, the environment, and the community.1 More specifically, medication adherence is the level of participation in a specific drug regimen once the patient agrees to that regimen.4 Improving medication adherence has the potential for a greater impact on the health of the population than improvements in medical therapy.7 Finances may be a barrier to adherence, especially for senior citizens on a fixed income. Programs to assess a patient’s ability to pay for medications and provide financial assistance if needed may improve medication adherence.6

Assessment

Medication adherence has been assessed using several different methods. Direct assessment methods (e.g., direct observation, laboratory assays of serum drug concentrations or biochemical markers) are the most accurate methods for assessing medication adherence, but they are costly, cumbersome, and often impractical.7 Patient or caregiver self-report is the most traditional indirect assessment method, especially in clinical settings.8 However, this method lacks reliability and validity because many patients are reluctant to admit that they are nonadherent for fear of upsetting the prescriber.

Prescription refill records are an alternative source of information about medication adherence provided the prescriptions are obtained from only one pharmacy.9 This method is not useful if a patient obtains refills from multiple pharmacies, a phenomenon that has become more popular with the recent increase in mail-order pharmacies. Moreover, prescription refill records do not necessarily reflect whether the medication actually was taken. A reliance on refill records may overestimate adherence.9 Pill counts may be conducted to circumvent the shortcomings of prescription refill records. However, pill counts traditionally are unreliable and tend to overestimate adherence.9,10 Electronic monitoring devices record the times when a prescription container was opened.9 However, the data do not necessarily reflect whether
the medication was taken.

Pharmacists can evaluate medication adherence and establish a system of checks and balances using multiple assessment methods. For pharmacists interested in this area, a direct patient interview is recommended initially, with prescription refill information used as a screening tool to detect possible non-adherence. This approach may not be feasible for patients who use mail-order pharmacies because a conversation with the patient usually is not possible.

Open-ended, nonjudgmental questions are recommended in conducting patient interviews. Such questions should address how and when the medications are taken, especially with respect to meals. The patient might be asked to explain or demonstrate how the medications are kept organized (e.g., in a pill box or organizer) and how the medications are taken. The pharmacist might offer to contact the prescriber on behalf of the patient and make suggestions to simplify the medication regimen. The pharmacist also could ask about the patient’s means for paying for medications and offer to help the patient obtain assistance with out-of-pocket expenses if available.

Patient interviews can be instrumental in identifying and correcting key medication-related problems. For example, when a patient receiving a bisphosphonate complained about gastrointestinal discomfort, she was asked to explain and demonstrate how she took the medication. She understood that she needed to take each dose at least 30 minutes before the first food or beverage of the day, take the medication with a full glass of plain water, and stand or sit upright for at least 30 minutes after the dose. In demonstrating how she took the medication, the patient placed a tablet on her tongue, took a sip of water from an 8-ounce glass, and set the glass down. The patient had not understood that she needed to drink the entire glass of water. The patient said that no one ever told her to drink the entire glass of water. This patient is like many others who take instructions (or lack thereof in this case) literally.

Medication nonadherence should be suspected in elderly patients whose functional abilities have deteriorated. Impairment in cognitive function, vision, or hearing can interfere with medication adherence.

### Chronic Diseases

Medication nonadherence is a problem associated with nearly all chronic diseases (Table 1), including terminal illnesses (e.g., late-stage cancer or chronic obstructive pulmonary disease). A complex medication regimen increases the likelihood of nonadherence.

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Mean (Range [%]) Medication Adherence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>80 (35-97)</td>
</tr>
<tr>
<td>Cardiovascular diseases (all)</td>
<td>71 (39-93)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73 (39-93)</td>
</tr>
<tr>
<td>Psychiatric illnesses</td>
<td>78 (75-83)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>70 (46-88)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>78 (76-80)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>73 (66-85)</td>
</tr>
<tr>
<td>Asthma</td>
<td>55 (37-92)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>51 (50-52)</td>
</tr>
</tbody>
</table>

* Adapted from reference 8.

The most common reason, by far, for failure to adhere to the medication regimen was the impression that the physician did not want the medication continued (59% on beta-blockers, 48% on ACE inhibitors, 50% on lipid-lowering agents, and 63% on aspirin), which may reflect miscommunication between the physician and patient. Problems with or fear of adverse effects, a desire to try another medication, inability to afford the medication, and a perception that the medication was unnecessary are other reasons for nonadherence, but none accounts for more than 18% of the sample. The investigators concluded that certainties properties beliefs about illness and medication use may be helpful in developing strategies to improve adherence.

Another chronic condition associated with poor adherence to therapy is Parkinson’s disease. Parkinson’s disease is a neurologic disorder with a profound physical and psychological impact, and antiparkinsonian drug therapies often cause adverse effects that can reduce adherence. Medication adherence was evaluated using electronic monitoring over a 3-month period in 54 patients with Parkinson’s disease. The average age was 62 years, 56% of patients were male, and 61% received levodopa therapy. Poor medication adherence (defined as less than 80%) was associated with a young age, receipt of a large daily number of tablets of antiparkinsonian medication, depression, and a poor quality of life. The investigators concluded that a triad of depression, medication underuse, and poor quality of life may be self-perpetuating in socially isolated patients with Parkinson’s disease.

In a study of a “silent disease,” hypertension, rates of unintentional and intentional adherence were explored using...
patient self-reports in a Veterans Affairs study of 558 patients.\textsuperscript{13} Unintentional nonadherence is a passive process, often arising from a patient’s carelessness or forgetfulness, and intentional nonadherence is an active process, whereby a patient deliberately chooses to deviate from the treatment regimen. The average patient age was 63 years, 98% of patients were male, and 42% of patients were nonwhite. Approximately 31% of patients reported unintentional nonadherence and 9% of patients reported intentional nonadherence. Unintentional nonadherence was associated with a nonwhite race and less than a 10th-grade education. Intentional nonadherence was associated with a nonwhite race and 5 or more adverse effects. The investigators speculated that these patients may have decided to stop their drug therapy because the perceived benefits did not outweigh the many adverse effects. The investigators also concluded that different strategies are needed to overcome unintentional and intentional nonadherence problems because of the different patient characteristics associated with these 2 types of nonadherence.

Involuntary (i.e., unintentional) and voluntary (i.e., intentional) nonadherence also were evaluated in a study of 40 patients with inflammatory bowel disease (a diagnosis of Crohn’s disease or ulcerative colitis).\textsuperscript{14} The average patient age was 40 years and 50% of the patients were male. Two thirds of patients reported involuntary nonadherence, including 60% who blamed forgetfulness and 38% who attributed it to carelessness. Voluntary nonadherence was acknowledged by 35% of patients, including 25% who stopped taking the medication because they felt worse after taking it and 15% who stopped taking the medication because they felt better after taking it.

### Postmenopausal Osteoporosis

Postmenopausal osteoporosis is a chronic disease, and adherence to drug therapy used to manage the disease is as much of a challenge as it is in other chronic illnesses. Adherence to 3 different osteoporosis medications (hormone-replacement therapy [HRT], the bisphosphonate alendronate, and the selective estrogen receptor modulator raloxifene) was evaluated in 956 women with low bone mineral density (BMD) who were interviewed an average of 7 months after treatment initiation.\textsuperscript{15} The average patient age was 45 years. The rate of discontinuation of HRT (26%) was significantly higher ($P = 0.02$) than the discontinuation rates for alendronate (19%) and raloxifene (19%). Discontinuation was more likely in women with bothersome adverse effects or who thought that their BMD test results did not show osteoporosis. There were no significant differences between treatments in adherence after adjusting for adverse effects and patient characteristics.

In a retrospective study of more than 58,000 patients who initiated drug therapy for osteoporosis (estrogen alone, estrogen plus a progestin, a bisphosphonate, or raloxifene), the overall 1-year compliance rate was less than 25%.\textsuperscript{16} The average duration of continuous therapy was 221 days for raloxifene, 245 days for the bisphosphonate, 262 days for estrogen alone, and 292 days for estrogen plus a progestin ($P < 0.0001$). Compliance was associated with significant reductions in the risk of hip (odds ratio [OR] = 0.382, $P < 0.01$) and vertebral (OR = 0.601, $P < 0.05$) fractures, use of physician services ($P < 0.0001$), hospital outpatient services ($P < 0.05$), and hospital care ($P < 0.01$) compared with noncompliance.

Other studies also have shown a link between osteoporosis medication adherence and patient outcomes. In 11,249 women with osteoporosis and a mean age of 68 years who were followed for 2 years, there was a 16% lower fracture rate ($P = 0.004$) in adherent women who took at least 80% of doses of their osteoporosis medications compared with nonadherent women.\textsuperscript{17} Another study examined 6,825 women aged 45 years or older with a diagnosis of postmenopausal osteoporosis. Forty-eight percent were refill compliant, and 21% were persistent. The relative risk of fracture was 26% less in compliant women than in noncompliant women ($P < 0.0001$), and 21% lower in persistent women than in nonpersistent women ($P < 0.0069$).\textsuperscript{18} In another study of postmenopausal women with low BMD, adherence to
osteoporosis treatment 1 year after initiation of therapy correlated with a significant increase in hip BMD (P = 0.01) and cross-linked N-teleopeptide of type I collagen (uNTX, P = 0.002) but not in the lumbar spine (P >0.05).19 Additionally, in a study of postmenopausal women who were patients in a multispecialty practice affiliated with a health maintenance organization, those with compliance greater than or equal to 66% showed significant increases in spine (P <0.005) and hip (P <0.004) BMD.20

A study conducted in the Netherlands involving 8,845 women who were at least aged 50 years and who initiated use of bisphosphonates found that adherence to bisphosphonate therapy reduced the risk of hospitalization for fractures by 20% to 30%.21 The protective effect was greatest (30%) in patients who used bisphosphonates consistently for more than 1 year.

Research is needed to evaluate whether patient preferences for bisphosphonates that are administered monthly instead of weekly or daily (see the preceding article by O’Connell in this supplement) translate into greater adherence for long periods (i.e., improved persistence) and improved patient outcomes.22 Studies currently are under way to explore these outcomes.

### Strategies

There are 3 key requirements for improving adherence to osteoporosis drug therapy. First, patients must be educated about the disease and its treatment and must believe that the disease is a personal threat. Second, patients need to see evidence of the rationale for and positive results from treatment (e.g., BMD test results).19 Third, health care providers need to take into consideration patient preferences (e.g., preferences for weekly or monthly doses instead of daily doses, concerns about adverse effects).

Efficacy usually takes priority over adverse effects and ease of medication administration, especially in patients with terminal illnesses. However, patients with nonterminal but chronic illnesses may be willing to compromise efficacy to avoid adverse effects. Positive reinforcement of adherence by such patients to the medication regimen is also vital.

The results of diagnostic testing provide justification for and motivation to adhere to osteoporosis treatment. When 1,014 patients who underwent diagnostic bone densitometry testing were surveyed about their knowledge of the test results, only 80% of the patients had been informed about the results. Only 63% of the 341 participants with a normal BMD, 31% of the 309 patients with osteopenia, and 50% of the 364 patients with a diagnosis of osteoporosis reported the results correctly.23 Patients with a low BMD (i.e., osteopenia or osteoporosis) who were able to correctly report their results were significantly more likely to have received a medication and continue to take it than patients who incorrectly reported their results.

Various strategies may be used to optimize medication adherence.24 Screening for indicators of nonadherence, including missed appointments and skipped prescription refills, can help identify problems.7 Strategies to improve adherence may involve counseling patients about the importance of the planned treatment regimen, enlisting the support of the patient’s family and friends, sending reminders about follow-up appointments, recognizing and reinforcing adherence efforts, simplifying the treatment regimen, addressing patient concerns about adverse effects, and maintaining a supportive provider-patient relationship.24 In addition, simple, clear instructions should be provided to patients about how and when to take medications. Input from the patient about his or her preferences should be elicited and accommodated to the extent possible.

Monitoring of drug therapy by nurses or other staff should be considered. Monitoring of raloxifene therapy in women with postmenopausal osteoporosis by nurses using a predefined protocol has been shown to improve patient adherence.19

### Theoretical Basis for Behavioral Change

The concept of self-management of chronic illness has been in the medical literature for many years and forms a solid theoretical basis for improving adherence.25 The individual patient must claim responsibility for self-care and accept the fact that he or she has a chronic illness and that treatment may improve his or her health status. Self-management involves making day-to-day decisions about one’s own care, and self-management education teaches problem-solving skills.26 Self-efficacy—the confidence to carry out a behavior needed to achieve a desired goal—is central to self-management.27 Adherence is likely to improve in patients with or at risk for osteoporosis if they embrace this self-management approach.

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**FIGURE 1 Measuring the Stage of Change for Osteoporosis Medication Adherence**

1. People sometimes find it difficult to take their medication as directed by their physician. As directed means consistently taking the amount of medication prescribed at the time prescribed. Please find the statement below that best describes the way you feel right now about taking your osteoporosis medication as directed.

   A. No, I do not take my osteoporosis medication as directed right now, but I am considering taking my osteoporosis medication as directed.
   B. No, I do not take my osteoporosis medication as directed right now, but I am not considering taking my osteoporosis medication as directed.
   C. No, I do not take my osteoporosis medication as directed, but I am planning to start taking my osteoporosis medication as directed.
   D. Yes, right now I consistently take my osteoporosis medication as directed.

2. If the response to question #1 is D, how long have you been taking your osteoporosis medication as directed?

   A. 3 months
   B. <3 months to 6 months
   C. >6 month to 12 months
   D. >12 months

Response 1A = precontemplation, 1B = contemplation, 1C = preparation, 1D and 2A or 2B = action, 1D and 2C or 2D = maintenance.

* Adapted from reference 29.

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**Osteoporosis Medication Adherence**

1D and 2A or 2B = action, 1D and 2C or 2D = maintenance.
Medication Adherence: A Challenge for Patients With Postmenopausal Osteoporosis and Other Chronic Illnesses

Adhering to prescribed osteoporosis drug therapy involves behavioral change, and readiness to change varies from one individual to another. Health-related behavioral changes are preceded by 5 stages of change (Table 2) that reflect readiness and motivation to change, according to the Transtheoretical Model of Change described years ago by Prochaska, based on a health-belief model. An individual may pass through all 5 stages of change quickly and implement the change promptly or spend a long time in a particular stage and fail to progress through subsequent stages.

A validated 2-item measure of the stage of change for medication adherence developed for patients with hypertension or human immunodeficiency virus infection might be adapted for patients with or at risk for osteoporosis (Figure 1). Efforts to improve medication adherence should be tailored to the stage of change for an individual (i.e., his or her readiness and motivation to change). [29]

■ Conclusion

Adherence to osteoporosis medications is less than optimal. Medication nonadherence can adversely affect patient outcomes and increase health care utilization and costs. An individualized approach to improving medication adherence based on patient preferences and readiness to change is needed.

REFERENCES


Therapeutic Options in the Prevention and Treatment of Postmenopausal Osteoporosis

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This continuing education activity as a whole provides 2.0 hours (0.2 CEU) of continuing education credit (program number 204-000-06-428-H01).

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Posttest Worksheet: Therapeutic Options in the Prevention and Treatment of Postmenopausal Osteoporosis

1. Which of the following is a risk factor for postmenopausal osteoporosis?
   a. Hypertension
   b. Smoking
   c. Obesity
   d. Use of hormone therapy

2. Which of the following BMD testing methods is most reliable to establish a diagnosis of osteoporosis?
   a. Central quantitative computed tomography (QCT)
   b. Peripheral QCT
   c. Central dual energy X-ray absorptiometry (DXA)
   d. Peripheral DXA

3. Which of the following designations applies to a T-score of -2.4?
   a. Normal
   b. Osteopenia
   c. Osteoporosis
   d. Established osteoporosis

4. Which of the following statements best characterizes the use of laboratory tests of urinary and serum collagen type 1 cross-linked N-telopeptide in patients with postmenopausal osteoporosis?
   a. They are markers of bone resorption used for assessing response to osteoporosis treatment.
   b. They are markers of bone formation used for assessing response to osteoporosis treatment.
   c. They are markers of bone resorption that can be used for the diagnosis of osteoporosis.
   d. They are markers of bone formation that can be used for the diagnosis of osteoporosis.

5. Which of the following calcium salts is preferred because of its low cost?
   a. Calcium carbonate
   b. Calcium chloride
   c. Calcium citrate
   d. Calcium gluconate
6. Which of the following is the National Academy of Sciences recommendation for adequate intake of elemental calcium for a woman aged 55 years?
   a. 800 mg/day
   b. 1,000 mg/day
   c. 1,200 mg/day
   d. 1,300 mg/day

7. Which of the following is the National Academy of Sciences recommendation for adequate intake of vitamin D for a woman aged 55 years?
   a. 200 units/day
   b. 400 units/day
   c. 600 units/day
   d. 800 units/day

8. Which of the following is the primary goal of interventions to prevent and treat osteoporosis in a woman aged 68 years?
   a. Optimize peak bone mass
   b. Accelerate bone formation
   c. Prevent accelerated bone loss
   d. Prevent bone loss, falls, and fractures

9. Which of the following osteoporosis drug therapies is unique because it promotes bone formation by osteoblasts and increases bone connectivity?
   a. Bisphosphonates
   b. Calcitonin salmon
   c. Raloxifene
   d. Teriparatide

10. Which of the following osteoporosis treatments is preferred in a patient with a hip T-score of -2.6?
    a. A bisphosphonate
    b. Calcitonin salmon
    c. Raloxifene
    d. A bisphosphonate, calcitonin salmon, or raloxifene may be used (none of these options is preferred)

11. If a patient complains of GI irritation from a daily bisphosphonate regimen, which one of the following would be the correct action to take?
    a. Verify that usage instructions are followed correctly
    b. Switch to a product that can be administered once weekly or once monthly
    c. Reinforce usage directions and switch to a once-weekly or once-monthly bisphosphonate
    d. Switch to raloxifene

12. Which of the following is a potential advantage of using an injectable bisphosphonate over an oral bisphosphonate?
    a. Is useful in patients with serious GI disease
    b. Requires less frequent home administrations
    c. Fewer adverse drug reactions
    d. Lower cost

13. Which of the following osteoporosis medications may reduce bone pain and analgesic medication requirements?
    a. Calcitonin salmon
    b. Denosumab
    c. Ibandronate
    d. Teriparatide

14. Which of the following osteoporosis medications should not be used in combination with bisphosphonates because the bisphosphonate may reduce its effects?
    a. Calcitonin salmon
    b. Estrogen-replacement therapy
    c. Raloxifene
    d. Teriparatide

15. Treatment for a woman with the following characteristics would result in cost savings if she were to use alendronate for 5 years:
    a. Aged 55 years, T score -2.0
    b. Aged 65 years, T score -2.0
    c. Aged 65 years, T score -2.7
    d. Aged 75 years, T score -2.5
    e. Aged 85 years, T score -3.0

16. Which of the following terms most closely reflects the length of time a medication regimen is continued?
    a. Adherence
    b. Chronicity
    c. Compliance
    d. Persistence

17. Which of the following is a direct method for assessing medication adherence?
    a. Electronic monitoring devices
    b. Patient self-reports
    c. Pill counts
    d. Serum drug concentration assays

18. Which of the following is a limitation of using pill counts for assessing medication adherence?
    a. High cost
    b. Impracticality
    c. Lack of reliability
    d. Tendency to underestimate adherence
19. Which of the following is the most likely reason for unintentional (i.e., involuntary) nonadherence to drug therapy for a chronic illness?
   a. Bothersome adverse effects
   b. Failure to appreciate the potential benefits of drug therapy
   c. Feeling better after taking the drug
   d. Forgetfulness

20. Which of the following is the first stage of change in health-related behavior in which the patient has no intention of changing, according to the Transtheoretical Model of Change?
   a. Contemplation
   b. Maintenance
   c. Precontemplation
   d. Preparation

21. Identifying the stage of change for osteoporosis medication adherence is important because
   a. it can affect the incremental cost-effectiveness ratio for drug therapy.
   b. it can be used to individualize strategies to improve adherence.
   c. it can justify the added expense of using a costly drug therapy.
   d. it can predict the reliability of adherence assessments.

To complete this continuing education activity, go to the ASHP Advantage CE Processing Center at www.ashp.org/advantage/ce to access the posttest and evaluation.