Challenges and Opportunities in Managing Osteoporosis Care

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Osteoporosis, a potentially devastating and debilitating disease, is a public health threat in the United States, as pointed out by Surgeon General Richard Carmona.[1] Osteoporosis and the fractures it causes have significant physical consequences, including limited mobility, deformity, and chronic pain, as well as functional limitations, such as a loss of independence. Fractures and osteoporosis also have serious psychosocial outcomes that can include anxiety, depression, loss of self-esteem, and the lack of rewarding social roles.

The prevalence of osteoporosis and low bone mass in the United States is substantial. More than 51 million American women and men have, or are at serious risk of developing, osteoporosis.[2] Although virtually any adult aged >50 years can develop low bone mass and fractures, certain individuals are at higher risk. Postmenopausal Caucasian women are at greatest risk; according to Kanis and colleagues,[3] nearly 50% of these women will have a fragility fracture after age 50 years. Postmenopausal women of all races have substantial risk of this disease. Although some may believe that osteoporosis is a disease that only affects women, this is simply untrue. Approximately 2 million men have a diagnosis of osteoporosis, with another 12 million at risk.[4] Estimates suggest that approximately 20% of men aged >50 years will have a fragility fracture before they die.[5]

Although low bone mass diagnosed as osteoporosis is serious, the truly life-changing outcomes seen in these patients result from fragility or osteoporotic fractures. The most common sites for these fractures are the vertebrae (spine), proximal femur (hip), and distal forearm (wrist).[2] Each year, approximately 2 million fractures occur in the United States at an annual cost of $17 billion.[6] Because our population is aging, and age is a major risk factor for fractures, we can expect the number of fractures per year to triple by 2040.[2]

Osteoporosis-related fractures have a substantial impact on mortality.[7] Up to 20% of individuals experiencing a hip fracture will die within the following 12 months. Vertebral fractures also increase mortality. According to Cauley et al,[8] women who have a hip or clinical vertebral fracture have a 6- to 9-fold increase in mortality. Perhaps as important is that fractures beget fractures.[9] In fact, a prior fracture increases the risk of another fracture by 86%.[10]

Practical issues in the diagnosis and treatment of osteoporosis

Despite the serious consequences associated with osteoporosis, this disease remains highly underdiagnosed and undertreated. Only 3% to 5% of patients with a hip fracture are treated for osteoporosis, and only 3% of patients with a wrist fracture receive or are recommended for a bone mineral density (BMD) test.[11] With respect to vertebral fractures, only 12% are diagnosed and, of these, only 2% are treated.[12] The situation is made worse by a trend over the past few years of a declining number of osteoporosis prescriptions.[13] According to Wysowski and Greene,[13] "An estimated 21.3 million prescriptions for oral bisphosphonates were dispensed in U.S. retail pharmacies in 2002 that increased 46% to a peak of 31.0 million in 2007 and 2008, and declined by 53% in a four year-period to 14.7 million in 2012." These trends underscore the importance of raising awareness among physicians to recognize at-risk patients in their practices, utilize appropriate diagnostic tools, and choose appropriate pharmacologic therapy.

Screening and diagnostic considerations

Diagnosis of a patient with suspected osteoporosis should begin with a complete medical history, including risk factors such as age at menopause, estrogen therapy after menopause, a family history of fracture (especially hip fracture), personal history of fracture after 45 years of age, falls, and medications known to cause or be associated with fracture (eg, glucocorticoid use, thyroid hormone, and antihypertensives; see the National Osteoporosis Foundation [NOF] website publication for list of medications and conditions that increase risk of osteoporosis in the recently updated *Clinician's Guide*[2]). **TABLE 1** includes a list of nonmodifiable and potentially modifiable risk factors for osteoporosis. Additional risk factors for osteoporosis include inadequate intake of calcium and vitamin D, lack of weight-bearing exercise, smoking, alcohol intake of more than 3 drinks per day, malabsorption, and other conditions predisposing to bone loss (eg, celiac disease, renal and liver disease, and rheumatoid arthritis).[2]

In addition to evaluating the main organ systems, the physical examination should also focus on the neck for thyroid masses and on the rest of the body for signs of a Dowager hump, Cushing syndrome, and systems related to increased risk of frailty and falling (eg, eyes, ears, muscle strength, gait, and reflexes); 50% of hip fractures in the elderly are related to falls. Height measurement on a stadiometer still remains invaluable, since a documented loss of height of 1.5 inches or more is very suggestive of a vertebral compression fracture.[14]

Diagnostic blood tests include the standard chemistries, but particular attention should be paid to renal function utilizing the estimated glomerular filtration rate (eGFR), since the bisphosphonates (BPs) are not approved for use in patients whose creatinine

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TABLE 1 Risk factors for osteoporotic fractures[1]

Nonmodifiable factors	Potentially modifiable factors
Personal history of fracture as an adult	Current cigarette smoking
History of fracture in first-degree relative	Low body weight (<127 lb)
Caucasian race	Estrogen deficiency
Advanced age	Early menopause (<45 years) or bilateral oophorectomy
Female sex	Prolonged premenopausal amenorrhea (>1 year)
Dementia	Low calcium intake (lifelong)
Poor health/frailty	Alcoholism
	Impaired eyesight despite adequate correction
	Recurrent falls
	Inadequate physical activity
	Poor health/frailty

clearance is below 35 mL/min. Other tests of note are serum calcium and 24-hour urinary calcium, which provide an indication of daily calcium intake as well as detection of hypercalciuria and hypocalciuria. Because of widespread vitamin D insufficiency/deficiency (defined as either <20 ng/mL or ≤12 ng/mL, respectively, depending on the professional guidelines), obtaining a serum 25(OH)D is very important. Obtaining a serum thyroid-stimulating hormone level is also advised, since hyperthyroidism may be not obvious clinically.

In diagnosing osteoporosis, the gold standard today is dual x-ray absorptiometry (DXA).[15] Dual x-ray absorptiometry is accepted as the best diagnostic method, not only to predict the future risk of fracture, but also to monitor patients on or off therapy. However, DXA does not measure bone quality or bone architecture. Other potential drawbacks of DXA include issues with positioning of the patient, repeat measurement on the same machine, standardization with acceptable coefficients of variation, artifacts from calcium tablets in the gastrointestinal (GI) tract, and currently, a severe reduction in reimbursement for the technology from insurance carriers. There are other technologies available, but these are largely research tools (eg, high resolution peripheral quantitative computed tomography [QCT]). Recommendations by the NOF for people who should undergo BMD testing include women aged ≥65 years and men aged ≥70 years, regardless of clinical risk factors; younger postmenopausal women; women in the menopausal transition; men aged 50 to 69 years with clinical risk factors for fracture; adults who have a fracture after age 50 years; and adults with a condition (eg, rheumatoid arthritis) or taking a medication (eg, glucocorticoids) associated with low bone mass or bone loss.[2]

Recommendations from the United States Preventive Services Task Force (USPSTF) are somewhat different. The USPSTF recommends screening for osteoporosis in women aged ≥65 years and in younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors. The USPSTF concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men.[16]

The criteria for the diagnosis of osteoporosis are accepted as a T score ≤–2.5 or osteopenia (ie, T score of –1 to –2.5 with a fracture).[2] However, treatment initiation is not dependent solely on the T score, because patients with osteopenia or even normal bone density can sustain fractures. In recent years, the World Health Organization (WHO) Fracture Risk Algorithm (FRAX) was introduced as a tool to evaluate a patient's absolute risk for osteoporotic fracture and to identify patients who would benefit from treatment. Risk factors used in FRAX are listed in **TABLE 2**.[17] According to the US-adapted WHO algorithm, a 10-year probability of a hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥20% are criteria used to initiate treatment (**TABLE 3**).[2] This algorithm is available online (http://nof.org/hcp/resources/865) and is often incorporated into DXA reports.

FRAX is a well validated tool, yet there are certain limitations associated with its use. These include dose of glucocorticoids, exclusion of falls, bone turnover markers (BTM), diabetes, and using the FRAX score in patients on, or who have been treated with, anti-osteoporosis drugs. All of these factors may impact utility. Other treatment algorithms for osteoporosis have predictability similar to FRAX and may be less laborious to use.[18]

Nonpharmacologic interventions for osteoporosis

Calcium and vitamin D supplementation

Several universal recommendations apply to all adults with or at risk of osteoporosis. An adequate amount of daily calcium and vitamin D are strongly recommended for all adults but especially for women aged >50 years and men aged >70 years who are at risk of osteoporosis. Recently, data have supported the idea that dietary calcium is preferable to supplemental calcium, and there have also been recent disputes about the optimum daily intake as well as whether supplemental nondietary calcium or supplemental vitamin D is harmful to the cardiovascular system.[19] However, Cauley and colleagues,[20] in a 5-year study after the Women's Health Initiative (WHI), found that calcium and vitamin D appeared to have no impact either way on mortality.

The NOF recommends that men aged 50 to 70 years consume 1000 mg per day of calcium and 800 to 1000 international units (IU) of vitamin D and that women aged ≥51 years and men aged ≥71 years consume 1200 mg per day of calcium and 800 to 1000 IU daily of vitamin D.[2] These levels are the same as those recommended in the 2010 Institute of Medicine (IOM) reference article for calcium and similar for vitamin D (IOM recommends 800 IU of vitamin D daily).[21] However, the USPSTF recommenda-

TABLE 2 Risk factors used in FRAX[17]

- Age
- Sex
- Ethnicity
- Body mass index
- Personal history of fragility fracture
- Parental history of hip fracture
- Current smoking
- Glucocorticoid therapy
- Rheumatoid arthritis
- Secondary osteoporosis
- Alcohol (>3 units/day)
- Femoral neck bone mineral density

Abbreviation: FRAX, Fracture Risk Algorithm.

TABLE 3 Criteria for treatment of osteoporosis[2]

- Hip or vertebral fracture
- T score ≤–2.5 at the femoral neck, total hip, or lumbar spine
- Low bone mass *and* 10-year probability of hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥20%

tions are very different. The USPSTF concluded that the current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men. The USPSTF concluded that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with greater than 1000 mg of calcium and 400 IU of vitamin D for the primary prevention of fractures in noninstitutionalized postmenopausal women. The USPSTF recommends against daily supplementation ≤1000 mg of calcium and ≤400 IU of vitamin D because there is no benefit for the primary prevention of fractures in noninstitutionalized postmenopausal women.[22] The USPSTF did not differentiate calcium and vitamin D needs for those with or at risk of osteoporosis. The Task Force may have been strongly influenced by the findings of the WHI.[23] When prescribing an anti-osteoporotic drug, it is important to ensure adequate calcium and vitamin D intake and not to administer anti-osteoporotic agents if the patient is hypocalcemic or if vitamin D deficiency is suspected until the patient is replete.[24]

Exercise

Complete coverage of exercise recommendations for those with osteoporosis is beyond the scope of this article. However, the NOF website has outstanding exercise recommendations (http://nof.org/articles/238).

The 2 types of exercise necessary for bone health are weight-bearing and muscle-strengthening exercises. Weight-bearing exercises help build bone and keep bones strong.[25,26] Strength training or resistance training helps to improve strength, balance, and flexibility. Perhaps its most important contribution is in preventing falls.[27] Unfortunately, drawing evidence from research in this area is difficult for a variety of reasons. Clinical trials of exercise have widely different participant populations, heterogeneous outcomes and measures, and are insufficient in the description of the precise exercises and how they are used. Some suggest that the impact of strength training is minimal in older adults, and more creative use of core strength training and Pilates exercise training will bring better results.[27] Until further research is conducted, knowledge about the impact of exercise on multiple aspects of osteoporosis is still insufficient.

Pharmacologic treatment considerations for osteoporosis

Every physician has a number of choices when choosing an appropriate treatment for a patient with osteoporosis. However, the challenge is to identify the optimal drug for the individual patient and tailor therapy to each patient's preference and tolerance.[28,29] Broadly speaking, the available therapies for osteoporosis fall into 2 categories: (1) those that inhibit bone resorption (antiresorbers, the largest and most frequently prescribed group) and (2) those that promote new bone formation (anabolics).

Historically, the introduction of the nitrogen-containing BP class of compounds radically altered the therapeutic approach to osteoporosis. Prior to 1995, the primary treatment available was estrogen. Overall, the BPs have demonstrated very robust fracture reductions and have a very long safety profile. Individual BPs do differ in their dosages, routes of administration, and some side effects, which may be more common with individual formulations; there are also more drugs in the BP class than in any other.[30]

Although the following discussion on pharmacologic treatment will focus mainly on the BPs, which are considered first-line therapy for osteoporosis and are the most widely prescribed agents not only in the United States but globally, we will also consider all medications approved for the prevention and/or treatment of postmenopausal osteoporosis.[31,32] This list includes selective estrogen receptor modulators (SERMs), hormones, parathyroid hormone (PTH) therapy, and a receptor activator of nuclear factor-kappa beta ligand (RANKL) inhibitor.[2] **TABLE 4** provides a list of the US Food and Drug Administration (FDA)-approved treatments.

Pharmaceutical options for prevention and treatment of osteoporosis

Antiresorptive: bisphosphonates

(Note: See section on BP concerns for more information about drug holidays, osteonecrosis of the jaw [ONJ], and atypical femur fractures.)

Alendronate sodium (Fosamax, Binosto), the first approved agent for the prevention and treatment of postmenopausal osteoporosis, is considered the gold standard of therapy for this disease. It is also the most widely prescribed antiresorptive for treatment of osteoporosis globally and has been clinically studied for over 18 years. Alendronate sodium has also been subsequently approved for treatment of glucocorticoid-induced osteoporosis, male osteoporosis, and in the elderly. The most common side effects are: upper GI irritation; severe bone, joint, and muscle pain; ONJ; and atypical femur fractures.[33] It is important to note, however, that ONJ is extremely rare. According to the American College of Rheumatology, "The number of ONJ cases in patients taking bisphosphonates by mouth is estimated to be between 1 in 1,000 and 1 in 100,000 for each year of exposure to the medication."[34] A similar finding about atypical femur fractures was noted by Shane and colleagues[35] in the 2010 American Society for Bone and Mineral Research (ASBMR) report:

TABLE 4 FDA-approved osteoporosis treatments[2]

Antiresorptive therapy	Anabolic therapy
Bisphosphonates	Teriparatide (PTH 1-34, Forteo)
Alendronate (Fosamax, Binosto)	
Risedronate (Actonel)	
Ibandronate (Boniva oral and IV)	
Zoledronic acid (Reclast IV)	
Estrogen agonist/antagonists	
Raloxifene (Evista)	
Estrogen/estrogen-progestin combinations	
Calcitonin	
Miacalcin	
Fortical	
RANKL inhibitor	
Denosumab (Prolia)	

Abbreviations: FDA, US Food and Drug Administration; IV, intravenous; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor-kappa beta ligand.

"…these fractures are rare, particularly when considered against the incidence of common osteoporotic fractures of all types."

Although there is reason to be concerned about these 2 side effects, physicians and patients should recognize that they are infrequent occurrences in those taking osteoporosis treatments. For those with trouble swallowing, a novel liquid formulation of alendronate sodium—identical to the molecule found in Fosamax (alendronate sodium)—has been approved for the treatment of osteoporosis. This formulation is taken as a buffered effervescent solution with only 4 ounces of plain water and may confer a significant advantage for the considerable number of patients who cannot or prefer not to swallow tablets.[35]

Risedronate (Actonel) was introduced shortly after alendronate and is available as a weekly and monthly oral preparation.[36] This agent has also demonstrated fracture reduction in postmenopausal women with osteoporosis and has long-term safety. Bone biopsies show no abnormal bone mineralization on histomorphometry. Risedronate is approved for the prevention and treatment of postmenopausal osteoporosis, treatment for osteoporosis in men, and prevention and treatment of glucocorticoid-induced osteoporosis.[37] Like alendronate, risedronate has as its most common side effects: upper GI irritation; severe bone, joint, and muscle pain; ONJ; and atypical femur fractures.[37] Again, both ONJ and atypical femur fractures are relatively rare in patients taking risedronate.[34,38]

Ibandronate (Boniva) is another oral (FDA-approved for prevention and treatment of postmenopausal osteoporosis) and intravenous (IV) (FDA-approved for treatment of postmenopausal osteoporosis) BP preparation, which is dosed at monthly intervals orally (150 mg) and 3-month intervals intravenously (3 mg). The BMD increases and bone marker reduction demonstrated after 2 years are similar to that of alendronate.[39] The most common side effects are upper GI irritation; severe bone, joint, and muscle pain; ONJ; and atypical femur fractures.[40] Ibandronate delivered by injection has no upper GI side effects, although it has ONJ, atypical femur fracture, and anaphylaxis as potential side effects.[40]

Zoledronic acid (Reclast) is the most potent BP and is given by an IV infusion annually at a dose of 5 mg diluted in dextrose saline. The clinical trials of zoledronic acid demonstrated significant fracture reductions at the spine, hip, and nonvertebral sites.[41] The recurrent fracture trial showed that zoledronic acid was effective in reducing spinal and nonvertebral fractures following a hip fracture.[42] Although the infusion eliminates problems with upper GI irritation as a side effect, zoledronic acid has the following possible side effects: severe bone, joint, and muscle pain; ONJ; and atypical femur fractures.[43]

Note: The oral BPs have rigid and specific guidelines for administration: first thing in the morning on an empty stomach with a full 8-ounce glass of tap water; no additional food or drink for 30 to 60 minutes; and no lying down for 60 minutes. Studies on compliance and persistence with osteoporosis medication suggest that these requirements are responsible for at least some of the poor compliance seen with these medications.[44]

Other antiresorptive medications for osteoporosis

Raloxifene (Evista) is an estrogen agonist/antagonist (formerly known as a SERM) approved for the prevention and treatment of postmenopausal osteoporosis.[45] It has been shown to reduce the risk of vertebral fractures and has an advantage over BPs in that it can be taken at any time of day. Raloxifene is also indicated for reduction in risk of invasive breast cancer in postmenopausal women who have osteoporosis or a high risk for invasive breast cancer. This drug has a black-boxed warning because it increases the risk of venous thromboembolism and death from stroke.[46]

Denosumab (Prolia) is an agent in a new class of antiresorptive drugs that is a fully human monoclonal antibody that targets the RANKL. RANKL, a cytokine member of the tumor necrosis factor family, is the principal final mediator of osteoclastic bone resorption. Denosumab prevents RANKL from binding to its receptor on the surface of osteoclasts and their precursors, thereby inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. Denosumab is approved for use in women with treatment-resistant postmenopausal osteoporosis and for the treatment of bone loss in men with osteoporosis. It is administered by subcutaneous injection at 6-month intervals.

In a 36-month trial, denosumab proved very effective in decreasing the risk of fractures at the spine, hip, and nonvertebral sites. Denosumab showed a 32% decrease (95% confidence interval [CI], 20% to 42%) in clinical osteoporotic fractures.[47] Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX.[48] The most common side effects in the trial were skin infections.[49]

Calcitonin (Miacalcin, Fortical) is a synthetic hormone used for the treatment of osteoporosis in postmenopausal women at least 5 years past menopause. Although it appeared to prevent vertebral fractures, its more common use was to control pain associated with acute fractures.[50] Calcitonin was first marketed as an injectable medication, but since a nasal spray became available, the injectable has not been widely used. The efficacy of calcitonin was found to be significant in a randomized controlled trial; it significantly reduced the risk of new vertebral fractures by 33% compared with placebo.[51] Recently oral calcitonin was studied to determine its utility in osteoporosis.[52] However, the trial did not show a statistically significant treatment effect.[53]

Estrogen/hormone therapy (multiple brands) was one of the first treatments for osteoporosis. It was widely used and showed effectiveness by increasing bone density at the spine and hip and by reducing hip, vertebral, and nonvertebral fractures. Estogen/hormone therapy was also used to manage menopausal symptoms, and was widely used prior to the release of the WHI study findings in 2002. This trial found that estrogen/hormone therapy was effective at reducing hip fractures and preventing colon cancer, but that unexpectedly, women taking estrogen or estrogen plus progestin were found to have statistically significantly higher rates of cardiovascular disease, stroke, dementia, breast cancer, and other conditions that were studied. The investigators concluded that health risks associated with estrogen/hormone therapy outweighed the benefits.[54]

As a result of these findings, estrogen's status was changed by the FDA. It is currently approved for the prevention of osteoporosis in women who are also experiencing menopausal symptoms. In cases where women do not have such symptoms, they should use another agent for the prevention of osteoporosis.[55]

Anabolic agents for osteoporosis

Teriparatide (PTH 1-34, Forteo) is an anabolic, approved for the treatment of severe osteoporosis in postmenopausal women, that showed very robust fracture reduction at vertebral and nonvertebral sites in clinical trials.[56] This drug has a black-boxed warning because of the preclinical incidence of osteosarcoma in rats, although no increased osteosarcoma incidence has been reported in postmarketing surveillance of patients who received this agent.[57] It is administered as a subcutaneous injection 20 mm

daily in conjunction with calcium and vitamin D for 24 months. After the treatment period is completed, the patient may have to be maintained on another therapy, since the benefit of teriparatide wanes quite rapidly within 6 months to 1 year following discontinuation. Teriparatide has been studied in nursing home patients and was found to be safe and effective.[58] However, there are few data suggesting it is actually being used, perhaps because of the need for a daily injection.

Future osteoporosis medications

Newer drugs for the treatment of osteoporosis have been evaluated in recent clinical trials. Odanacatib, an inhibitor of cathepsin K (a proteinase believed to play a vital role in bone resorption and remodeling), decreased bone resorption, maintained bone formation, and increased BMD in a randomized, double-blind, 2-year trial of postmenopausal women.[59]

AMG 785 is a monoclonal antibody targeted against sclerostin, an osteocyte-secreted protein that negatively regulates osteoblasts and inhibits bone formation. In a randomized, double-blind, placebo-controlled trial in healthy men and postmenopausal women, AMG 785 demonstrated dose-related increases in bone-formation markers and significant increases in BMD.[60]

Commentary on bisphosphonate use

As noted, safety and side effect issues with BPs are of significant concern to patients and physicians alike, including: (1) risk for atypical fractures; (2) the question of how long to treat a patient with a BP (also referred to as a drug holiday); and (3) risk for ONJ. Atypical fractures, although rare, became a prominent concern for patients and physicians and led to a decline in the use of BPs. The FDA and the ASBMR published an initial report in 2010 that addressed some of these concerns, followed by an update in 2013. The second report by the ASBMR Task Force on atypical subtrochanteric and diaphyseal femoral fractures includes revisions to the original case definition of atypical femoral fracture (AFF) and a review of studies specific to AFFs.[38] This report contends that, while the relative risk of AFFs for patients taking BPs is high, the absolute risk of AFFs in patients on BPs is low (3.2 to 50 cases per 100,000 person-years). However, long-term use of BPs may be associated with higher risk (~100 per 100,000 person-years). The criteria used to assist in diagnosis of AFF are as follows:

Major criteria

- Minimal trauma
- Lateral origin with transverse orientation
- Complete fractures through both cortices with medial spike or incomplete fracture with lateral cortex involved[33]
- Noncomminuted or minimally comminuted
- Localized periosteal or endosteal thickening of the lateral cortex at fracture site (beaking)

Minor criteria

- Generalized increase in cortical thickness of the femoral diaphysis
- Unilateral or bilateral prodromal symptoms in groin or thigh
- Bilateral complete or incomplete femoral diaphysis fractures
- Delayed fracture healing
- The incidence does appear to increase with increasing years of use (>5 years)

Atypical fractures as a side effect were subsequently described in the package inserts of all BPs. However, numerous publications are in agreement that, despite this rare occurrence, the benefits far outweigh the risks and should not preclude BPs from being prescribed.[61] Although there are no published guidelines on treatment, there is universal agreement that once an atypical fracture has occurred, the antiresorptive drug should be stopped.

The debate about the length of treatment with a BP was fuelled by the findings of the Fracture Intervention Trial Long-Term Extension (FLEX) study, which showed that after 5 years of treatment, stopping alendronate did not result in further spinal BMD loss over the ensuing 5 years.[62] However, patients who did continue therapy for an additional 5 years had further significant increases in BMD at the spine, as well as significant reductions in clinical vertebral fractures. If the T score at the femoral neck still remained <–2.5 after 5 years of treatment, continued therapy with alendronate resulted in a significant reduction in nonvertebral fractures. In the FLEX trial, the investigators showed that women with very low bone mass continued to receive benefits from remaining on alendronate. Additional research will be necessary before we can make definitive recommendations about the duration of BP use by individuals.[63]

An FDA report in May 2012, which directed that treatment should be stopped after 3 to 5 years unless the patient is high risk, led to discontinuation of BP therapy by many physicians. This author's practice is to continue treatment for another 5 years in patients considered high risk (eg, an incident fracture or past history of a fracture, a T score of –2.5 at the hip, and aged ≥75 years [when hip fracture increases dramatically]), and assess the patient with a DXA at 2-year intervals. If the patient has received zoledronic acid IV for 3 years, the patient is assessed and generally the same criteria are used whether to continue or stop therapy. If the decision is made to stop therapy based on the patient's progress, this should be considered a "drug holiday" and not termination. The patient should be followed periodically and, if necessary, based on BMD or BTM changes, measured at timely intervals and have treatment reinstated.

The rare condition of ONJ has also led to unnecessary patient concerns with BP use. Osteonecrosis of the jaw is defined as an oral cavity lesion characterized by 1 or more spots of bare alveolar or hard palate bone, in the absence of local malignancy or radiation therapy to the head or neck. The characteristics include the lesion not healing and persisting for 6 to 8 weeks, and the mechanism by which ONJ occurs is currently uncertain.[64] Current estimates of ONJ prevalence have ranged from 0.001% to 0.01% among oral BP-treated populations.[65] Because of the confusion surrounding this disorder, including patients being refused dental procedures if they are currently taking a BP, the American Dental Association published recommendations in November 2011 on the management of patients receiving antiresorptive therapy.[66] In it, the authors state, "The risk for developing antiresorptive agent–induced osteonecrosis of the jaw (ARONJ) remains unknown despite attempts at quantification." It does appear, however, that early reports of ONJ incidence and prevalence were exaggerated.

Treatment success: compliance and persistence with osteoporosis medications

Nine FDA-approved pharmaceutical therapies currently exist for osteoporosis, an important increase since 1995. However, regardless of the type or efficacy of the medication, it can only work if patients take it. Unfortunately, many patients do not regard osteoporosis as a serious or chronic disease and do not take their medication as prescribed.[67] Compliance (the consistency and accuracy with which a medication is initially followed) and persistence (the length of time a regimen is continued) are the most challenging aspects of osteoporosis management, both for patients who must take the medication and for physicians who

treat this disorder.[68,69] Noncompliance to osteoporosis medication ultimately undermines the reason for taking medication and leads to the outcome of fracture. Indeed, a positive correlation exists between compliance to osteoporosis medication and lower fracture risk, as evidenced by a study of more than 11,000 postmenopausal women with osteoporosis. A 16% lower fracture rate occurred in adherent women who took at least 80% of the doses of their osteoporosis medications compared with noncompliant women.[70]

One way in which patients do not comply with medication prescriptions is called secondary nonadherence. In this case, patients fill their prescriptions, take them home, and start to take them. Then something happens (eg, side effects, cost, forgetfulness) and the patients are no longer following their prescribed medication routine. Many studies have examined secondary nonadherence in osteoporosis and interventions have been developed to improve patient medication behavior, although many have been ineffective.[71-73]

Until recently, primary nonadherence to osteoporosis therapy has been ignored by both the clinical and research communities. Primary nonadherence occurs when a health care provider orders a medication for a patient, and the prescription is never picked up by the patient. A study of over 8000 women with a new BP prescription showed that nearly 30% of women did not pick up their prescription within 60 days.[74] Results of this study also revealed that older age and emergency department utilization were associated with increased odds of primary nonadherence, and that prescribers practicing 10 or more years had lower odds of primary nonadherent patients compared with providers practicing less than 10 years.

The factors that contribute to osteoporosis medication noncompliance are numerous and may be patient-, treatment-, or physician-related. Because of the largely silent, asymptomatic nature of osteoporosis, patients may have little or no motivation to take medication for it.[75] Moreover, patients who are not informed about the potential benefits of osteoporosis treatment are less likely to be adherent. The complexities associated with taking oral BPs (ie, medication must be taken 30-60 minutes before breakfast with a full glass of water and patient must remain upright for at least 30 minutes) are considered inconvenient by some patients. Failure to comply with these dosing instructions may result in esophagitis or other GI adverse events.[76] Some evidence exists to show that less frequent dosing of medication can improve patient compliance.[77,78] Other studies find that weekly doses are taken more frequently than monthly doses.[79] Regardless of the dosing interval or the medication delivery system, the poor level of compliance and persistence with these medications suggests that health care professionals may not truly be "treating" osteoporosis.

What can be done to improve medication behaviors in osteoporosis? Greater communication between patients and health care providers can improve compliance and persistence, which can be accomplished through emails and phone calls, in addition to regular office visits. Consistent follow-up with the patient through visits, emails, and phone calls is essential for assessment of treatment tolerance and adherence. In a study that examined the effect of nurse monitoring on adherence to osteoporosis therapy in postmenopausal women, monitoring of patients increased adherence to therapy by 57% at 1 year.[80] Physicians who work with their patients to identify and resolve barriers that contribute to nonadherence, and who educate and empower patients in self-managing their medications, may help improve overall treatment adherence and facilitate positive treatment outcomes.

Summary

Osteoporosis is a serious disease with a prevalence that is expected to increase as the population ages. This disease deserves the attention of both patients and physicians, especially since very effective means exist for identifying and assessing patients at risk for osteoporosis. Fractures are the endpoint of the fragile bone and have a significant morbidity and mortality. A number of safe and effective therapies, which can reduce fractures by approximately 50% at all sites, are available to treat osteoporosis. It is incumbent on physicians to identify at-risk individuals and implement appropriate therapy. Because medication adherence remains an important issue in osteoporosis, education and attention to patient preferences for medications may help prevent the fractures that lead to the negative outcomes of osteoporosis. ●

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Binosto®
(alendronate sodium) effervescent tablet for oral solution **70 mg**

BINOSTO® (alendronate sodium) effervescent tablets for oral solution 70 mg

INDICATIONS AND USAGE

BINOSTO® (alendronate sodium) effervescent tablets for oral solution 70 mg is a bisphosphonate indicated for the treatment of osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis.

Important Limitations of Use
The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture reevaluated periodically.

IMPORTANT SAFETY INFORMATION

BINOSTO is contraindicated in patients with the following conditions:
- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes
- Increased risk of aspiration
- Hypocalcemia
- Hypersensitivity to any component of this product. Hypersensitivity reactions including urticaria and angioedema have been reported

Upper Gastrointestinal Adverse Reactions can occur. Instruct patients to follow dosing instructions. Discontinue if new or worsening symptoms occur. Hypocalcemia can worsen and must be corrected prior to use. *Severe Bone, Joint, Muscle Pain* may occur. Discontinue use if severe symptoms develop. *Osteonecrosis of the Jaw* has been reported. *Atypical Femur Fractures* have been reported. Patients with new thigh or groin pain should be evaluated to rule out a femoral fracture. *Sodium Content*: Each tablet contains 650 mg sodium, equivalent to 1650 mg NaCl. Use caution in patients on sodium restriction.

In clinical trials, the most common adverse reactions (incidence greater than or equal to 3%) are abdominal pain, acid regurgitation, constipation, diarrhea, dyspepsia, musculoskeletal pain, and nausea.

Calcium supplements, antacids or oral medications containing multivalent cations interfere with absorption of alendronate. Use caution when co-prescribing aspirin/nonsteroidal anti-inflammatory drugs that may worsen gastrointestinal irritation. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain, or new or worsening heartburn) they should stop taking BINOSTO and consult their physician.

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