AN EVIDENCE-BASED APPROACH TO OSTEOPOROSIS MANAGEMENT

Christina Barrington, PharmD*

ABSTRACT

In an effort to step up fracture prevention efforts, the National Osteoporosis Foundation (NOF) has released a revised guide on the comprehensive management of osteoporosis, which includes detailed recommendations on assessment and diagnosis, in addition to a summation of treatment options. This article includes updated NOF recommendations, pharmacoeconomic considerations of assessing fracture risk, and a review of currently available antiresorptive and anabolic agents. Essentially, the NOF recommends bone mineral density (BMD) testing in all women aged 65 and older and in men aged 70 and older. Beyond BMD measurements, additional skeletal health assessment techniques are available, one of which is the World Health Organization fracture risk algorithm (FRAX), which calculates the 10-year probability of a major fracture and is thus used to identify high-risk candidates for pharmacologic intervention. Currently available treatments are largely assessed on their efficacy in reducing vertebral and, most importantly, nonvertebral (hip) fractures, with bisphosphonates having the most abundant data on fracture reduction.


*Pharmacy Director, Health Alliance Medical Plans, Urbana, Illinois.
Address correspondence to: Christina Barrington, PharmD, Pharmacy Director, Health Alliance Medical Plans, 301 South Vine Street, Urbana, IL 61801. E-mail: christina.barrington@healthalliance.org.

Efforts to reduce the long-term consequences of osteoporosis are dependent not only on the effectiveness of current pharmacologic therapies, but most critically, on the ability to identify and treat at-risk individuals before their bone mineral density (BMD) becomes dangerously low and fractures become inevitable. The majority of fractures actually occur in patients with low bone mass rather than osteoporosis, and although currently available treatments are effective in secondary prevention of subsequent fractures, they cannot reverse the disability and mortality that is well known to accompany hip fractures. As a reflection of the essential need to step up fracture prevention efforts, especially in the face of a rapidly growing elderly population, the National Osteoporosis Foundation (NOF) has, in collaboration with other societies (eg, World Health Organization [WHO]), released a revised guide on the comprehensive management of osteoporosis. Since publication of the original guide in 1999, the NOF has ascertained that many patients are not given adequate prevention information and appropriate testing, therefore, many of the new recommendations, particularly those pertaining to risk assessment and diagnostic testing, are based largely on the WHO 10-year fracture model (discussed later in this article) and an accompanying economic analysis. The following discussion focuses on key NOF recommendations.

ASSESSMENT

The NOF recommends that all postmenopausal women and older men be evaluated for osteoporosis risk (to determine the need for BMD testing) and risk factors for falls (eg, personal history of falling, visual deficits, and dehydration), which are responsible for the majority of fractures. Many lifestyle choices (eg, high caffeine intake, alcohol, and smoking), disease
states (e.g., endocrine disorders, gastrointestinal [GI] disorders, and hypogonadal states), and medications (glucocorticoids, anticoagulants, and chemotherapy) impact bone remodeling and are, therefore, considered to be risk factors for osteoporosis (see previous article by Elena M. Umland, PharmD). In general, the more risk factors that are present, the greater the risk of a fracture.

Because BMD has been shown to correlate with bone strength and is a vital predictor of future fracture risk, the diagnosis of osteoporosis is established by measurement of BMD, or by the presence of a low-trauma fracture in at-risk individuals. The BMD values corresponding to normal or low bone mass, osteoporosis, and severe or established osteoporosis are based on the WHO diagnostic classification, which is included in the Table. Essentially, the NOF recommends BMD testing in all women aged 65 and older and in men aged 70 and older. In general, BMD measurements are not routinely recommended in healthy young men or premenopausal women, unless specific risk factors are present.

**INTEGRATING PHARMACOECONOMICS INTO ASSESSMENT TOOLS**

Beyond BMD measurements, additional skeletal health assessment techniques are available, one of which is the WHO fracture risk algorithm (FRAX). Developed from studying population-based cohorts from various parts of the world, this algorithm uses femoral neck (or total hip) BMD and specific risk factors to calculate the 10-year probability of a hip fracture and any major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture). Essentially, FRAX is designed to identify high-risk candidates for pharmacologic intervention, and as such, it has been used in a US-specific cost-effectiveness analysis to identify the level of absolute fracture risk at which treatment becomes cost effective. Taking into account estimates of incidence, morbidity, mortality, and costs related to fractures in the United States, treatment was found to be cost effective ($600/year drug cost for 5 years with a 35% fracture reduction) when the 10-year hip fracture probability reached approximately 3%. Translating this risk into more clinical terms, it would be cost effective to treat patients who have experienced a fragility fracture, those with osteoporosis defined by WHO criteria, older individuals at average risk, and patients with osteopenia who have additional risk factors. This pharmacoeconomic analysis is particularly relevant in response to the expected increase in fracture incidence among the rapidly growing geriatric population, and it also endorses existing clinical practice recommendations.

**PHARMACOLOGIC THERAPY**

Patients considered for treatment should be counseled on risk factor reduction, as well as the importance of calcium, vitamin D, and exercise. Medications used for osteoporosis can be divided into 2 categories: drugs that inhibit osteoclast activity (antiresorptive agents) and drugs that stimulate osteoblast activity (anabolic agents). With the exception of teriparatide, currently marketed therapies are considered antiresorptive and include bisphosphonates, the estrogen agonist/antagonist (EAA) raloxifene, calcitonin, and estrogen. The NOF guidelines include information on these agents, but make no recommendations in regard to preference of therapy.

**BISPHOSPHONATES**

The bisphosphonates alendronate, risedronate, ibandronate, and zoledronic acid are nitrogen-containing compounds that bind to mineralized bone sur-

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**Table. Defining Osteoporosis by BMD**

The World Health Organization has established the following definitions based on BMD measurement at the spine, hip, or forearm by DXA devices:

| Normal: BMD is within 1 SD of a “young normal” adult (T-score at -1 and above) |
| Low bone mass (“osteopenia”): BMD is between 1 and 2.5 SD below that of a “young normal” adult (T-score between -1 and -2.5). |
| Osteoporosis: BMD is 2.5 SD or more below that of a “young normal” adult (T-score at or below -2.5). |

Patients in this group who have already experienced 1 or more fractures are deemed to have severe or “established” osteoporosis.

Note: Although these definitions are necessary to establish the presence of osteoporosis, they should not be used as the sole determinant of treatment decisions.

BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; SD = standard deviation.
faces, where they are taken up by osteoclasts and ultimately inhibit bone resorption by interfering with key enzymes needed for osteoclast development and life span.6 From all the data that have accumulated over the past 10 to 15 years on the efficacy of bisphosphonates, the largest body of evidence demonstrating antifracture effects has come from studies of risedronate and alendronate, each of which has been shown to reduce vertebral and, most importantly, non-vertebral (including hip) fractures by 20% to 50% in postmenopausal women with osteoporosis.6 These agents have also been shown to prevent vertebral fractures in men with osteoporosis (alendronate) and in glucocorticoid-treated patients (risedronate and alendronate). As a result, alendronate and risedronate are generally preferred bisphosphonates for the treatment of postmenopausal and secondary osteoporosis. Trends toward fewer fractures are apparent within months of initiation of these agents, before substantial increases in BMD have occurred.5 The newer bisphosphonate, zoledronate, has also been shown to reduce vertebral and non-vertebral fractures, but the older agents (ibandronate, etidronate, and clodronate) have not been demonstrated to prevent non-vertebral fractures.6,7

In regard to long-term efficacy of bisphosphonates, data available on patients treated with alendronate for up to 10 years suggest that its beneficial effects may be sustained after cessation of therapy, provided that a sufficient cumulative dose has been reached. There are no definitive conclusions on the ideal duration of bisphosphonate therapy, but in studies of women who discontinued treatment with alendronate after 5 years, loss of BMD was slow and fracture incidence appeared to be similar to that of women who continued alendronate treatment after 5 years.8

**IMPROVING ADHERENCE WITH EXTENDED DOSING**

Intermittent (or less frequent than daily) dosing of bisphosphonates has gained favor as a result of the recognition that currently used agents may persist on the bone surface for considerable periods of time, and as part of an effort to improve patient adherence with therapy.6,9 Both compliance and persistence are considered poor in at least 50% and 80% of patients during the first year and after 3 years of osteoporosis treatment, respectively. Most cases of inadequate adherence occur within 3 months of starting therapy and are associated with relatively high rates of fracture.9 In over 3500 women treated with bisphosphonates, fracture rates in those who did not comply or persist with treatment were 20% to 30% higher than in patients persisting with medication as prescribed for 24 months. Conversely, fracture rates tend to be lower among patients with higher rates of prescription refills. Many women have expressed a preference for less frequent bisphosphonate dosing (weekly or monthly vs daily), and some studies have reported better (although still not optimal) compliance rates with less frequent dosing intervals.9 As a result, use of daily bisphosphonate dosage forms is receding in favor of weekly (ie, alendronate orally or risedronate orally), monthly (ie, ibandronate orally monthly or intravenous [IV] every 3 months, or risedronate orally), and even annual (ie, IV zoledronic acid) formulations (see also article by Mary Beth O’Connell, PharmD, BCPS, FASHP, FCCP, on longer acting bisphosphonates).1

Adverse effects are similar for all oral bisphosphonates and include upper GI irritation and mucosal ulceration, which justifies the need to refrain from lying down for 30 to 60 minutes after dosing.6 Although placebo-controlled trials of nitrogen-containing bisphosphonates did not demonstrate significant upper GI toxicity, post-marketing studies suggest that up to 10% of patients prescribed these agents experience such side effects.6 IV administration of bisphosphonates avoids upper GI toxicity, but may produce a transient, self-limited myalgic syndrome (particularly with zoledronate).6 More recently, the long-term safety of bisphosphonates has been questioned as a result of their association with unusual fractures and delayed healing (possibly due to oversuppression of bone turnover); however, long-term studies have not substantiated these concerns.10 There have also been reports of osteonecrosis of the jaw, but the majority of these cases have occurred with use of high-dose IV bisphosphonates in patients with multiple myeloma and metastatic skeletal malignancies, often following dental procedures.11

**RALOXIFENE**

The only EAA that is currently approved for prevention and treatment of osteoporosis in postmenopausal women, raloxifene, has estrogenic effects on some tissues (bone, lipid metabolism, and clotting cascade), and antiestrogenic effects on others (eg, uterine, endometrium, and breast).12 As a result of these selective actions, raloxifene is somewhat similar to estrogen in its protective effects on bone, but unlike
estrogen, it does not increase the risk of endometrial or breast cancer, and it does not appear to alter cardiovascular risks. In fact, one recent study of approximately 20,000 postmenopausal women with an increased risk of breast cancer found raloxifene to be as effective as tamoxifen in decreasing the risk of invasive breast cancer.13 In another study of approximately 10,000 postmenopausal women with, or at risk for, coronary heart disease, raloxifene had rather neutral cardiovascular effects (no decrease in risk of myocardial infarction, death from coronary causes, and hospitalization from acute coronary syndrome), but it did increase the risk of venous thromboembolism and fatal stroke.14 Raloxifene may also exacerbate vasomotor symptoms (hot flashes).

In regard to its efficacy in osteoporosis, raloxifene has not been found to reduce non-vertebral (hip) fractures, but it has been shown to reduce the risk of vertebral (spine) fractures by 30% and 55% in patients with and without a prior spine fracture, respectively.1 As a result of its lack of observed effects on hip fractures, raloxifene is not generally used as a first-line treatment, but it remains a viable choice for women who have contraindications to, or cannot tolerate, bisphosphonates, or those who have a high risk of breast cancer.15

**Teriparatide**

This agent is a recombinant form of parathyroid hormone (PTH) and is the only US Food and Drug Administration (FDA)-approved therapy that affects bone formation. Daily exposure to low-dose synthetic PTH has been shown to cause an anabolic effect on the skeleton, which includes new bone formation on trabecular and cortical bone surfaces via preferential stimulation of osteoblastic activity.16 Indicated for use in postmenopausal women and hypogonadal men with osteoporosis who are at high risk for fractures, teriparatide has been shown to reduce the risk of both vertebral and non-vertebral fractures by 65% and 53%, respectively.1 Anabolic therapy may provide significant benefits in patients with severe osteoporosis (especially those with previous fractures), and in individuals who cannot tolerate, or have had an inadequate response to, antiresorptive therapy.1,15 However, teriparatide requires subcutaneous injection, is relatively expensive (although cost effective in selected patients), and has safety concerns.16 Because animal carcinogenicity studies indicate a possible association between teriparatide and osteosarcoma, patients with an increased risk of this malignancy (eg, Paget’s disease of bone) and those having prior radiation therapy of the skeleton, bone metastases, hypercalcemia, or a history of skeletal malignancy should not receive teriparatide. Because teriparatide is only used for a maximum of 2 years, it is common practice to follow with an antiresorptive agent (ie, bisphophonate) to maintain or further increase BMD.1

**Calcitonin and Hormone Replacement Therapy**

For purposes of this discussion, both of these treatments are combined in this section because they each have significant drawbacks that limit their role in therapy. Available in nasal spray, subcutaneous injection, and oral dosage forms, calcitonin is an osteoclast inhibitor that has been found to have analgesic effects in acute vertebral fractures and is associated with a 33% decrease in the rate of new vertebral fractures among postmenopausal women with pre-existing vertebral compression fractures. However, because the agent exhibits modest effects on BMD and has not demonstrated efficacy in hip fractures, it is generally used as a third-line therapy.2

For many years, hormone replacement therapy (HRT) played a pivotal role in the prevention of postmenopausal osteoporosis, until the highly publicized Women’s Health Initiative (WHI) trial reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein phlebitis during 5 years of treatment with conjugated estrogens and medroxyprogesterone.17 Subsequent analysis of these data showed no increase in cardiovascular disease in women starting treatment within 10 years of menopause, and in the estrogen-only arm of WHI, no increase in breast cancer incidence was noted over 7.1 years of treatment. But because of the overall risks associated with HRT, the US FDA recommends that approved nonestrogen treatments be considered for osteoporosis.

**Conclusions**

The plethora of evidence on the effectiveness of currently available treatments for osteoporosis is certainly a testament of our ability to limit the long-term consequences of this disorder. But without proper and far-reaching risk assessment and diagnostic efforts, the disease will continue to thrive.
REFERENCES


