

The Female Patient[®]

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Osteoporosis: Screening and Diagnosis in Clinical Practice

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Women of all ages rely on their ObGyns for basic health care needs and yearly examinations. As female patients are accustomed to receiving annual Papanicolaou tests and referrals for yearly mammography screening, this annual visit represents an excellent opportunity to counsel women on the risks of osteoporosis and the importance of regular screening. It is also the

perfect time to evaluate patients for risk factors that may predispose them to bone fragility and a greater chance of fracture. With appropriate screening, diagnostic testing, counseling, treatment, and follow-up, osteoporosis can be prevented and the risk of osteoporotic fracture reduced. New guidelines from the National Osteoporosis Foundation (NOF) have been published to assist in this endeavor; the recommendations include a new fracture risk algorithm that is clinically useful for office practice.^{1,2}

Epidemiology

Of the 10 million Americans with documented osteoporosis, 80% are women, and 1 in 2 white women over the age of 50 will have an osteoporosis-related fracture in her lifetime.^{1,3} Although osteoporosis can affect adults of any age, hormonal changes associated with

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menopause are an important risk factor. With the overall aging of the US population, the postmenopausal stage of life will be extended and the prevalence of osteoporosis will likely increase. Osteoporosis and osteoporotic fractures have far-reaching implications as major causes of age-related disabilities requiring chronic care.

An additional 37% to 50% of

American women have low bone mass (osteopenia), a precursor to the development of osteoporosis.⁴ This large at-risk population is a prime target for screening and early treatment to prevent disease progression and reduce fracture risk. By explaining to patients that osteopenia and osteoporosis are “clinically silent” disorders, with no signs or symptoms of bone weakening until a fracture occurs, health care professionals can encourage postmenopausal women and other at-risk patients to undergo periodic screening to monitor bone mineral density (BMD), detect decreasing bone mass early, and initiate treatment with one of the available therapies for modulating bone turnover and increasing bone mass.

Risk Assessment and Screening

Both ACOG and the NOF recommend periodic BMD testing to screen for osteoporosis in all postmenopausal women aged 65 years and older and in all postmenopausal women who have sustained a fracture; such testing is the best way of determining

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risk and future management.^{1,4} Screening may also be advisable in postmenopausal women who have a medical condition that increases their risk for osteoporosis, but only if the results will influence therapeutic or patient management decisions.

The main determinant of a woman's maximum bone mass is genetics.⁴ Women with a family history of osteopenia or osteoporosis have a greater chance of developing these disorders with advancing age. In addition to family history and advancing age, risk factors for osteoporosis include female gender, low weight and body mass index, estrogen deficiency, and high alcohol intake (Table 1).⁴

Another significant risk factor is long-term low intake of calcium and vitamin D. Inadequate calcium intake for women over age 50 is less than 1,200 mg/d and insufficient vitamin D intake is less than 800 to 1,000 IU/d of vitamin D3. Other risk factors are limited physical activity, smoking, early cessation of menstruation, athletic amenorrhea, and overall poor nutrition. A loss of height found during physical examination may be due to the presence of osteoporosis or an undiagnosed fracture and should trigger an x-ray.

BMD Screening

Bone mineral density measurement performed by dual-energy x-ray absorptiometry (DEXA) scanning of the lumbar spine or hip remains the "gold standard" for osteoporosis screening and diagnosis. The

TABLE 1. Risk Factors for Osteoporosis^{1,4}

- Older age
- Female gender
- Low weight and body mass index
- History of fracture
- Low trauma fracture history
- Family history of osteoporosis
- Caucasian or Asian race
- Insufficient physical activity
- Estrogen deficiency (due to early menopause, bilateral oophorectomy, or prolonged amenorrhea in premenopausal women)
- Poor nutrition
- Smoking
- Long-term low calcium intake
- High alcohol intake

TABLE 2. Defining Osteoporosis by Bone Mineral Density*¹

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

- Normal: BMD is within 1 SD of a "young normal" adult (T-score ≥ -1)
- Low bone mass (osteopenia): BMD is 1 to 2.5 SD below that of a "young normal" adult (T-score -1 to -2.5)
- Osteoporosis: BMD is 2.5 SD or more below that of a "young normal" adult (T-score ≤ -2.5). Patients in this group who have already experienced one or more fractures are deemed to have severe (established) osteoporosis.

SD = standard deviation.

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

BMD values can detect low bone density before a fracture occurs, guide treatment decisions, and help predict risk of future fracture. A BMD measurement obtained by DEXA scanning is considered normal if it is within 1 standard deviation (SD) of the average value for a healthy young adult, which corresponds to a T-score of -1 or greater. Values that are 1 to 2.5 SD below the norm (T-scores between -1 and -2.5) are indicative of low bone mass, and a T-score of -2.5 or less confirms a diagnosis of osteoporosis (Table 2). One SD below normal equals a loss of 10% to 15% of bone mass; thus, a patient with a T-score of -2.5 has lost more than 25% of her bone mass.

The Fracture Risk Algorithm

The updated NOF guidelines have added a new predictive measure to the clinician's toolkit for assessing osteoporotic fracture risk. The Fracture Risk Algorithm (FRAX), generated by the World Health Organization (WHO), enables health care professionals to calculate a patient's probability of having a major osteoporotic fracture (vertebral, hip, forearm, or humerus) over a 10-year period.² The algorithm uses population-based cohort studies in Europe, North America, and Australia. It has been modified and fine-tuned for use in the United States by applying US fracture and mortality rates.¹ The FRAX tool relies on economic models devised to determine the 10-year risk for hip or major osteoporotic fracture, above which it becomes cost-effective to initiate pharmacologic treatment.

FIGURE. The FRAX tool is on the Web at www.shef.ac.uk/FRAX.

Unique FRAX algorithms are available for four categories of US women: white, black, Hispanic, and Asian-American. The FRAX questionnaire elicits information on a patient's age, sex, weight, height, adult fracture history (either spontaneous or associated with trauma), history of parental hip fracture, current smoking behavior, and alcohol intake. Also included are questions on oral glucocorticoid use, established rheumatoid arthritis, and "secondary osteoporosis."²

For example, when using the FRAX calculator, a woman aged 68 with a weight of 120 pounds and a femoral neck BMD T-score of -2.4 would show a 10-year risk of major osteoporotic fracture of 32% and a 10-year risk of hip fracture of 5.1% (Figure). This exceeds the NOF fracture risk cut-off recommendations for starting treatment for osteoporosis, which are 20% and 3%, respectively. (Note that the FRAX tool can calculate the metric conversions for height and weight.)

Diagnostic Dilemma

Underdiagnosis of osteoporosis and osteoporotic fracture is a major problem in the United States and globally. Fewer than 25% of high-risk patients in the United States—defined as persons aged 67 years or

older with a recent fracture—undergo BMD testing or receive medication for osteoporosis.⁵ Risk assessment for osteoporosis and referral for BMD screening every 2 years (or more frequently if new risk factors arise) should be a core component of a woman's annual gynecologic examination. This visit also presents an ideal opportunity to counsel patients on the importance of adequate calcium and vitamin D intake and regular physical activity to maintain bone health and prevent loss of bone mass.

A large proportion of vertebral fractures may be clinically silent, with no apparent signs or symptoms, contributing to the high prevalence of undetected osteoporosis. In a subanalysis of a multinational, prospective trial, 2,451 postmenopausal patients with newly diagnosed osteoporosis were screened for vertebral fractures based on

both central and local radiography.⁶ At least one vertebral fracture was detected in 32% of these patients.

The study had a high false-negative rate, as 34% of the vertebral fractures noted by the central reader were not recognized in reports from the local radiologists. A single vertebral fracture was detected in about 50% of the patients with false-negative screening results. Among the other 50%, radiographic evidence revealed more than 1 fracture.

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When to Treat

Osteoporosis is associated with significant morbidity and health care expense. However, it remains underdiagnosed and undertreated, even after an osteoporotic fracture has occurred. A population-based study revealed that treatment within 6 months after hip fracture improved from 7% in 1995 to 31% in 2002.⁷ This trend did not continue, however, and in 2004 fewer than 33% of patients received pharmacologic treatment within 6 months of hip fracture.

The NOF recently developed new guidelines to assist physicians in making decisions regarding who to treat based on the identification of patients at high risk of fracture. These updated NOF guidelines incorporate the US-adapted FRAX model and specify that treatment should be considered in postmenopausal women aged 50 and older who present with any of the following:

- Hip or vertebral fracture
- Other prior fractures and low bone mass (osteopenia)
- T-score of -2.5 or less at the femoral neck, total hip, or spine after appropriate evaluation to exclude secondary causes
- Low bone mass and secondary causes such as glucocorticoid use
- Low bone mass and a 10-year probability of hip fracture of 3% or greater, or a 10-year probability of any major osteoporosis-related fracture of 20% or greater based on the FRAX calculation.

Conclusion

Osteoporosis and declining bone mass, primarily among postmenopausal women, are important pub-

ObGyns can play a key role in monitoring for risk factors of bone fragility and emphasizing the importance of periodic BMD screening.

lic health concerns. Osteoporosis contributes greatly to pain, disability, loss of independence, health care expenditures, and even death among elderly patients and at-risk younger women. Health care professionals—especially ObGyns—can play a key role in monitoring for risk factors of bone fragility and emphasizing the importance of periodic BMD screening. With

regular screening at 2-year intervals, a healthy lifestyle, and adequate intake of calcium and vitamin D, it is possible to help prevent loss of bone mass and the development of osteoporosis. For at-risk women or those with established osteoporosis, pharmacologic treatment options are available to prevent further bone weakening and disease progression.

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Pharmacologic Prevention and Treatment of Osteoporosis

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Obstetrician-gynecologists are in a uniquely favorable position to provide female patients with comprehensive bone health care, including prescribing effective treatments to slow the progression of osteoporosis and prevent osteoporosis-related fractures. Selecting a therapeutic regimen from among the various drug classes and medications approved for the treatment of osteoporosis requires an understanding of the advantages each drug offers, the risk of side effects, route of administration options, and dosing specifics. It is important to consider adherence issues that could compromise treatment success and to match dosing regimens and modes of delivery with patient needs and preferences. Effective implementation of a fracture prevention strategy depends on a combination of nonpharmacologic approaches to improving bone health, including exercise and adequate intake of calcium and vitamin D, appropriate pharmacologic therapy, and careful monitoring of compliance and response to treatment.

It is important to consider adherence issues that could compromise treatment success and to match dosing regimens and modes of delivery with patient needs and preferences.

When to Initiate Treatment

Newly updated guidelines issued by the National Osteoporosis Foundation (NOF) for the prevention and treatment of osteoporosis recommend the following criteria.¹ Bone mineral density (BMD) testing for:

- All women aged 65 and older
- Postmenopausal women with risk factors
- Women who have sustained a fracture (to determine degree of disease severity).

Initiation of treatment in patients with:

- Hip or vertebral fracture
- BMD T-score of -2.5 or less, measured at the femoral neck, total hip, or spine by dual-energy x-ray absorptiometry (DEXA) scanning
- Low bone mass (osteopenia, T-score of -1 to -2.5) at the femoral neck, total hip, or spine, and 10-year hip fracture probability of 3% or greater or overall major osteoporosis-related fracture probability of 20% or greater based on the US-adapted World

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Health Organization's Fracture Risk Assessment (FRAX) tool (Sidebar).^{2,3}

The new NOF *Clinician's Guide to Prevention and Treatment of Osteoporosis* can be read in its entirety on the Web at www.nof.org/professionals/Clinicians_Guide.htm.

The NOF recommends BMD testing every 2 years.¹ For women undergoing pharmacologic therapy for osteoporosis, a repeat DEXA scan should be performed 2 years after the initiation of

treatment and at subsequent 2-year intervals.¹

Age and hormonal status are clear determinants of osteoporosis risk. Underdiagnosis and undertreatment of osteoporosis in postmenopausal women are ongoing concerns, as use of FDA-approved pharmacologic therapies has been proven to reduce fracture risk. A study aimed at estimating the probability that treatment for osteoporosis would be initiated after hip fracture found that therapy was started in fewer than 33% of patients within 6 months after a fracture.⁴

SIDEBAR. How to Use FRAX

The World Health Organization developed the FRAX tool to predict a patient's 10-year risk of hip fracture or major osteoporotic fracture (including the spine, forearm, hip, or shoulder).² The FRAX algorithm takes into account BMD measurements at the femoral neck and individual risk factors to yield an absolute fracture risk. The NOF performed an economic analysis of the FRAX tool and determined that osteoporosis treatment would be cost-effective in patients with a 10-year hip fracture probability of 3% or greater or a 10-year probability of a major osteoporosis-related fracture of 20% or greater.¹ In its updated guidelines, the NOF recommends that clinicians evaluate patients for treatment using both the T-score and the revised FRAX algorithm that has been adapted specifically for use in the United States.¹ The FRAX tool is particularly useful for evaluating the large population of women with osteopenia and identifying which of these at-risk women are appropriate candidates for treatment to prevent the development of osteoporosis and reduce fracture risk.³ The FRAX tool is available at www.shef.ac.uk/FRAX.

While patients with documented osteoporosis should be offered treatment, the decision to initiate treatment in the setting of low bone mass (osteopenia) must be individualized, and should be based on an assessment of each patient's risk profile. Risk factors for osteoporotic fracture include:

- Family history of osteoporosis
- Personal history of falls and fracture
- Personal history of rheumatoid arthritis or other predisposing condition
- Low body mass index
- Estrogen deficiency/menopause
- Smoking
- High alcohol intake (3 or more drinks per day)
- Long-term glucocorticoid use.²

Regardless of whether a patient's BMD is osteopenic, osteoporotic, or normal or whether she is taking an approved therapeutic agent, it is crucial that health care professionals emphasize the importance of adequate daily calcium and vitamin D intake to all women. According to the 2004 US Surgeon General's report, *Bone Health and Osteoporosis*, women with inadequate intake of calcium or vitamin D should take nutritional supplements as needed.⁵ The current recommendations for postmenopausal women are a daily intake of at least 1,200 mg of calcium and 800 IU of vitamin D.

Hormone Therapy and Osteoporosis

Estrogen and combined estrogen/progestin therapy are effective for the prevention of osteoporotic fractures, both vertebral and hip/nonvertebral. The North American Menopause Society (NAMS) released a position statement presenting a consensus opinion on the role of hormone therapy (HT) in postmenopausal women, concluding: "Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms; to treat or reduce the risk of certain disorders such as osteoporosis or fractures in select postmenopausal women; or both."^{6,7} This conclusion was based on evidence derived from randomized, controlled clinical trials that show HT reduces postmenopausal osteoporotic fractures. The group recommends that extended use of HT should be an option for women with reduced bone mass, regardless of menopausal symptoms. The FDA advises that before using estrogen or combination HT solely for osteoporosis prevention, the physician should first consider using approved nonestrogen treatments.¹

The Women's Health Initiative (WHI) found that postmenopausal women aged 50 to 79 years who took estrogen plus progestin had a hip fracture rate of 10 per 10,000 person-years, compared with 15 per 10,000 for the placebo group—a significant 33% reduction.⁸ The decrease in the rate of other osteoporotic fractures (23%) in the WHI trial was also statistically significant.⁸ The clinical management guidelines issued by ACOG state that HT is most effective if initiated within the first 5 to 10 years after menopause, and that even if "started long after menopause, estrogen or hormone therapy produces substantial gains in bone mass."⁹ However, as the WHI study reported a significantly increased risk of cardiovascular events and breast cancer among women taking combined estrogen and progestin therapy,⁸ ACOG recommends that HT for osteoporosis or fracture prevention be considered on an individual basis, taking into account a woman's history and risk factors and the need for HT to treat menopause-related vasomotor symptoms.⁹

Overall, compliance with osteoporosis therapies is poor, so that simpler, less frequent dosing tends to be preferable to improve adherence and persistence.

Selecting a Treatment Approach

Pharmacologic classes for the prevention of osteoporotic fracture include bisphosphonates, selective estrogen receptor modulators (SERMs), and hormonal medications. All approved agents inhibit bone resorption except for teriparatide/parathyroid hormone (Forteo),

which stimulates new bone formation (Table 1).

In addition to efficacy, important factors to consider in selecting a treatment approach include barriers to adherence (taking a drug as prescribed) and persistence (continued use of a drug). Noncompliance has been described as "the Achilles' heel" of antifracture efficacy, as approximately 50% of patients either do not follow the prescribed treatment regimen or discontinue treatment within 1 year.⁹ In one study, patients who were highly compliant with bisphosphonate therapy had 18.7% ($P<0.05$) fewer fractures than poorly compliant patients over a 2-year period.¹⁰

A range of variables may affect adherence, including absence of disease-related symptoms, comorbid conditions, and dosing regimens/drug delivery.¹¹ Overall, compliance with osteoporosis therapies is poor, so that simpler, less frequent dosing tends to be preferable to improve adherence and persistence.¹⁰ Bisphosphonates are available in either oral or intravenous (IV) formulations; calcitonin can be administered intranasally; and teriparatide requires subcutaneous delivery.¹¹

TABLE 1. Efficacy of Drugs for Prevention of Osteoporotic Fractures¹¹

Drug (Brand)	Vertebral Fractures	Hip and/or Nonvertebral Fractures
BISPHOSPHONATES		
Alendronate (Fosamax) ^a	✓✓✓	✓
Ibandronate (Boniva)	✓✓✓	INSF
Risedronate (Actonel)	✓✓✓	✓✓
Zoledronic acid (Reclast)	✓✓✓	✓✓
SERMS		
Raloxifene (Evista)	✓	INSF
HORMONAL MEDICATIONS		
Calcitonin (Miacalcin, Fortical)	✓✓✓	INSF
Estrogen ^b (Premarin, Prempro, Premphase)	✓✓✓	✓✓
Teriparatide (Forteo)	✓✓✓	✓✓

^a Alendronate is now available in generic formulation.
^b The largest study of estrogen was the Women's Health Initiative, which included postmenopausal women with unknown bone mineral density.

✓ = effective for prevention of fractures with high or medium level of confidence; INSF = insufficient evidence; SERMs = selective estrogen receptor modulators.

TABLE 2. Treatments for Osteoporosis by Dose and Administration Route¹¹

Drug Name	Brand Name	Dose ^a	Route
BISPHOSPHONATES			
Alendronate ^b	Fosamax	10 mg daily	Oral
		70 mg once weekly	Oral
		70 mg once weekly	Oral solution
Ibandronate	Boniva	2.5 mg daily	Oral
		150 mg once monthly	Oral
		3 mg every 3 months	IV
Risedronate	Actonel	5 mg daily	Oral
		35 mg once weekly	Oral
		75 mg daily for 2 days/month	Oral
		150 mg once monthly	Oral
Zoledronic acid	Reclast	5 mg once yearly	IV
SERMS			
Raloxifene	Evista	60 mg daily	Oral
HORMONAL MEDICATIONS^c			
Calcitonin-salmon	Miacalcin Fortical	200 IU daily	IN
Estrogen ^a	Premarin	0.3 mg daily	Oral
Estrogen plus medroxyprogesterone ^a	Prempro	0.3 mg/1.5 mg daily	Oral
		0.45 mg/1.5 mg daily	Oral
		0.625 mg/2.5 mg daily	Oral
		0.625/5 mg daily	Oral
	Premphase	0.625 mg daily days 1-14 0.625 mg/5 mg daily days 15-28	Oral
Teriparatide	Forteo	20 mcg daily	SQ

^a Dosages are FDA approved for prevention of osteoporosis when nonestrogen medications are not considered to be appropriate.

^b Alendronate is now available in generic formulation.

^c Other hormonal routes of administration are available for the prevention of osteoporosis. A list of all hormone products for postmenopausal use is available at www.menopause.org/Portals/0/Content/PDF/htcharts.pdf.

IV = intravenous; IN = intranasal; SQ = subcutaneous; SERMs = selective estrogen receptor modulators.

Bisphosphonates are the most commonly prescribed treatments for osteoporosis, and offer patients a varied selection of dosing regimens (Table 2). Risedronate (Actonel, Actonel with calcium), and ibandronate (Boniva) are available as monthly pills. Alendronate (Fosamax, Fosamax plus D) is available as a weekly oral dose. Women who prefer less frequent dosing via IV administration can opt for ibandronate (Boniva, 3 mg every 3 months). Alternatively, the newest medication available—zoledronic acid (Reclast, 5 mg once yearly)—requires only a single annual infusion given over 15 minutes. Data have shown that during 3 years of use it reduces the incidence of spinal fractures by 70%, hip fractures by 41%, and nonvertebral fractures by 25%.¹²

The most common side effects reported by patients on oral bisphosphonates are gastrointestinal symptoms. Intravenous bisphosphonates can cause transient post-infusion symptoms such as low-grade fever and muscle aches. These symptoms can be reduced by administering acetaminophen after dosing. Estrogens and SERMs can cause venous thromboembolism.⁶⁻⁸ Other long-term risks of hormone therapies include breast cancer, heart attack, and stroke.⁶⁻⁸ Risks and side effects of bisphosphonates are covered on page 10 of this newsletter.

Adherence to dosing instructions is especially critical for the oral bisphosphonates, which are known to have relatively poor bioavailability. For example, the oral bioavailability of alendronate averages less than 1% when taken on an empty stomach with water followed by a 2-hour wait before eating or drinking.¹³ Decreasing the wait time before eating breakfast from 2 hours to 60 or 30 minutes reduces bioavailability by 40%, and taking the drug with or 2 hours after breakfast yields a greater than 85% decline in its bioavailability. Therefore, it is important to instruct patients on the need to take oral bisphosphonates after an overnight fast and to refrain from eating for 30 to 60 minutes after dosing. Oral bisphosphonates are contraindicated in women with uncorrected hypocalcemia, inability to sit or stand for 30 to 60 minutes, esophageal stricture or achalasia, or severe renal impairment.¹⁴

Conclusion

With the availability of effective drug therapies to reduce the risk of osteoporosis-related fractures and to slow or reverse the disease process, women at risk for osteoporosis and fracture will rely on their health care professional to recommend initiating treatment and to select the most appropriate pharmacologic agent from among the approved drug classes and medications. The choices vary in their route of deliv-

ery and dosing, ease of use, and risk of side effects and adverse events. Another key consideration in selecting a drug regimen is the likelihood of adherence, as proper administration of these agents—particularly the oral bisphosphonates—and continued use are absolutely critical for successful treatment outcomes. An understanding of the characteristics and advantages of each drug and of individual patient preferences should drive treatment selection.

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The Utilization of Intravenous Bisphosphonates

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Oral bisphosphonates have a well-established track record of effectiveness for preventing and treating osteoporosis and preventing osteoporotic fracture. Yet despite their efficacy and good tolerability if taken as directed, overall adherence (taking a drug as prescribed) to oral bisphosphonate drug regimens depends on the patient remembering to take a daily, weekly, or monthly medication on a long-term basis. Bisphosphonate drugs administered intravenously only once or several times a year offer an attractive option that can improve patient adherence and persistence (continued use of a drug), increasing the likelihood of treatment success and positive outcomes.

An intravenous (IV) bisphosphonate may be an appropriate choice when a patient prefers less frequent dosing.¹ Because an IV formulation must be administered by a health care professional, perhaps at an infusion center, use of an IV bisphosphonate ensures adherence for the indicated treatment period. Two IV bisphosphonates are FDA approved for the treatment of osteoporosis: ibandronate (Boniva) and zoledronic acid (Reclast). Dosing for IV ibandronate is 3 mg once every 3 months, and for IV zoledronic acid is 5 mg once yearly.

As ObGyns typically have a relationship with their patients that spans the reproductive and menopausal years, they are in a unique position to understand a woman's health habits, adherence history, and treatment preferences.¹ If adherence to an osteoporosis treatment that relies on oral bisphosphonate use is a concern, the physician should present the patient with alternative dosing and delivery options, including periodic IV drug infusion.

Ramifications of Poor Adherence

Rates of adherence and persistence with the oral bisphosphonates alendronate, risedronate, and ibandronate—and with other prescription and nonprescription agents used to treat osteoporosis—do not achieve

the desired levels for optimal effect in the population at risk.² This can greatly compromise therapeutic efficacy.

Among a study group of more than 35,000 women who received an oral bisphosphonate prescription, 57% were considered noncompliant based on their refill behavior.³ The 43% of women considered compliant with bisphosphonate therapy experienced a statistically significant 21% reduction in total fractures compared with the non-compliant group over the 2-year study period.

This same study also evaluated persistence with the drug regimen based on gaps in prescription refills.³ The results demonstrated that 80% of women did not persist with treatment as prescribed. For the other 20% of women with good persistence, their overall fracture rate was 29% lower, hip fracture was 45% lower, and vertebral fracture was 40% lower. These significant reductions in fracture rates underscore the importance of educating patients in the value of compliance with all aspects of oral dosing regimens and monitoring patients for both adherence and persistence.⁴

Bioavailability

Higher doses of oral bisphosphonates are prescribed because of their poor bioavailability. The body typically absorbs less than 1% of an oral dose. Patients must be told to take oral bisphosphonates after an overnight fast and not to eat or drink for at least 30 minutes after a dose. Zoledronic acid—when given via IV infusion—offers 100% bioavailability, as circulating drug levels are not dependent on gastrointestinal (GI) absorption. About 61% of the drug will bind directly to bone, while the remaining 39% is eliminated from the circulation within 24 hours.⁵ As zoledronic acid bypasses the GI tract, it not only eliminates absorption limitations but also avoids many of the prevalent GI side effects associated with oral bisphosphonate use.⁵ It is the high binding affinity and good bioavailability of zoledronic acid that allows it to be dosed once yearly.

Biochemical Markers of Bone Turnover

The ability of antiresorptive treatments for osteoporosis to suppress biochemical markers of bone turnover predicts their capacity to increase BMD.⁶

An IV bisphosphonate may be an appropriate choice when a patient prefers less frequent dosing.

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Oral and IV bisphosphonates significantly lower mean urine levels of *N*-telopeptide of type I collagen (NTx), a marker of bone resorption, into the premenopausal range.⁷

Fracture Risk Reduction With IV Bisphosphonates

In postmenopausal women with osteoporosis diagnosed based on BMD testing or prevalent vertebral fracture, IV zoledronic acid reduces the incidence of future fracture. The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) pivotal fracture trial evaluated the potential of IV zoledronic acid to decrease fracture risk in more than 7,500 postmenopausal women with osteoporosis in 27 countries over 3 years.⁸ Relative risk reduction compared with placebo was statistically significant for the incidence of new vertebral fracture (70% for morphometric fractures and 77% for clinical vertebral fractures), hip fracture (41%), clinical nonvertebral fracture (25%), and any clinical fracture (33%).⁸

Intravenous zoledronic acid use led to a significant increase in BMD over 3 years, with an increase in the mean percentage of change from baseline of 6.7% at the lumbar spine, 6% for the total hip, and 5.1% at the femoral neck.⁸ Additionally, patients taking IV zoledronic acid had significantly less height loss than those taking placebo.⁸

Another study, the HORIZON recurrent fracture trial, evaluated the efficacy of IV zoledronic acid compared with placebo to prevent future fractures following surgery to repair a low-trauma hip fracture.⁹ Use of IV zoledronic acid yielded a significant reduction in the relative risk of overall clinical fracture (35%) and of clinical vertebral fracture (46%), and significant increases in total hip BMD (6.4%) compared with placebo.⁹

Intravenous ibandronate, 3 mg once every 3 months, is more effective than oral ibandronate, 2.5 mg daily, at raising BMD in the spine and hip.¹ The mean increase in lumbar spine BMD after 1 year in patients treated with IV ibandronate was 4.5%, compared with 3.5% for patients taking daily oral ibandronate. Similarly, the mean increases from baseline in total hip BMD at 1 year were 2.1% for the injectable formulation and 1.5% for the oral drug. Oral ibandronate was shown in clinical trials to reduce the risk of vertebral fractures by 52%, but did not significantly reduce the risk of hip fractures. The FDA approval for the IV formulation

Intravenous zoledronic acid demonstrated a significant reduction in the incidence of new vertebral fracture (70% for morphometric fractures and 77% for clinical vertebral fractures) compared to placebo.

was based on the data from the oral formulation.

Adverse Events

No significant differences in rates of serious adverse events or discontinuation of treatment between IV zoledronic acid and placebo were reported in either of the HORIZON trials.^{8,9} In the HORIZON pivotal fracture trial, the incidence of serious adverse events was 29.2% in the zoledronic acid group and 30.1% in the placebo group.⁵ In the zoledronic acid group, 5.4% of patients withdrew from the

study due to adverse events, compared with 4.8% in the placebo group.

The most common adverse events reported within 3 days after infusion with zoledronic acid are fever, myalgia, flu-like illness, headache, and arthralgia.^{8,9} With regard to renal safety, transient increases in serum creatinine occurred in 1.8% of treated patients compared with 0.8% of patients given placebo. These elevated levels resolved without medical intervention and had no cumulative impact on renal function over 3 years.⁸

Atrial fibrillation has been described as a possible risk of bisphosphonate use, although the evidence is not conclusive. In the preliminary findings of its safety review, the FDA reported that it was not able to identify a population of bisphosphonate users at increased risk for atrial fibrillation, and advised practitioners not to change their prescribing practices.¹⁰

Another potential risk of bisphosphonate therapy is osteonecrosis of the jaw (ONJ).¹¹ This has primarily been reported in patients with advanced cancer and multiple risk factors for ONJ. Symptoms consistent with ONJ occurred in 1 patient treated with placebo and 1 patient given zoledronic acid in the HORIZON pivotal fracture trial, and both cases resolved with appropriate treatment.⁸ The HORIZON recurrent fracture trial reported no cases of ONJ.⁹ The risk of ONJ in patients with osteoporosis has been estimated as less than 1 in 100,000 patient-years.

Patient Selection, Referral, and Office Administration

Patients tend to prefer medications that require less frequent dosing. In a study of 128 postmenopausal women randomized to receive either oral alendronate, 70 mg weekly, or IV zoledronic acid, 5 mg once yearly, the majority of patients favored yearly IV therapy,

TABLE 1. Referral and Administration Process for IV Zoledronic Acid (5 mg)

Referring the Patient

- Confirm that serum calcium levels are in the normal range and estimated creatinine clearance is ≥ 35 mL/min
- Recommend the patient consume at least 1,200 mg calcium and 800 IU vitamin D daily
- Give patient a prescription for IV zoledronic acid, 5 mg (Reclast) infusion and referral information (an Infusion Center Locator tool is available at www.reclast.com)

Administering the Infusion

- Obtain IV zoledronic acid, 5 mg, from distributor (supplied ready-to-use)
- Use HCPCS “J” code: J3488 zoledronic acid, 1 mg; bill as 5 units
- For Medicare patients, bill under Part B; no effect on Part D “donut hole”

IV = intravenous; HCPCS = Healthcare Common Procedure Coding System.

TABLE 2. What Patients Can Expect With Zoledronic Acid Infusion

- Infusion of IV zoledronic acid involves a similar procedure to having a blood sample drawn, except that fluid is introduced instead of removed
- Patients should eat normally and drink at least 2 glasses of fluids before treatment
- The infusion will take at least 15 minutes, and can be done in a physician’s office or at an infusion center
- Normal activities may be resumed immediately after treatment
- After the first treatment, common side effects may include flu-like symptoms such as fever, muscle or joint pain, and headache, which typically resolve on their own or with a mild pain reliever such as acetaminophen; side effects are much less common after successive treatments

reporting it to be more convenient and stating that they would be more willing to take it for a long period of time.⁷ Similar results were reported in another study of 221 women, with nearly 79% preferring a once-a-year infusion, 9% expressing a preference for once-a-week oral dosing, and 11.8% considering the treatments to be equally appealing.¹²

There are several contraindications to the use of IV ibandronate or zoledronic acid. These include use of zoledronic acid in an oncology setting (Zometa), low blood calcium levels, kidney problems, allergy to ibandronate or zoledronic acid, and being pregnant or nursing or planning to become pregnant.

Health care professionals who prescribe IV bisphosphonates can either refer patients to an infusion center for administration, or the drug can be administered in the office setting if the office has infusion capabilities.

Coding for Zoledronic Acid Infusion

Claim Type	Coding System	Coding for Zoledronic Acid
Patient diagnosis	ICD-9-CM	733.01—Postmenopausal osteoporosis
Drugs & Biologics	HCPCS	J3488—Injection, zoledronic acid (Reclast), 1 mg*
	NDC	0078-0435-61 5 mg/100 mL
Professional Services	CPT®	90765—Intravenous infusion for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; HCPCS = Healthcare Common Procedure Coding System; NDC = National Drug Code; CPT = Current Procedural Technology.

* Bill as 5 units.

Table 1 suggests a referral and administration process for the clinician prescribing IV zoledronic acid, and Table 2 suggests information that the patient should be given in preparation for the infusion process.

Conclusion

Osteoporosis is a serious public health problem, and it is clear there is a need for varied management options to ensure the greatest possible patient adherence and compliance. Although a variety of medications are available to slow bone loss and improve bone health, none is ideal, with problems that include low compliance, undesirable side effects, and inconvenient dosing regimens. Oral delivery of bisphosphonates is safe, effective, and well tolerated, but depends on patient adherence and persistence with the oral regimen. Bisphosphonates delivered via IV infusion require administration as infrequently as once a year, thus ensuring compliance and optimal dosing over a 12-month period.

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Counseling Patients on the Management of Osteoporosis

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The clinician's role in maintaining skeletal health includes counseling patients regarding prevention, screening, and treating this silent condition. Because there are usually no symptoms, patients may be less concerned than they are about more clinically evident diseases. However, patient education information on osteoporosis is abundant, and clinical management is well defined. Care should be based on the many practice guidelines available from groups such as ACOG and the Agency for Healthcare Research and Quality (AHRQ), with the most recent ones issued by the National Osteoporosis Foundation (NOF) and North American Menopause Society (NAMS).¹⁻⁴ Although these organizations' guidelines differ in minor ways, the central message is the same, focusing on lifestyle measures (nutrition and adequate calcium/vitamin D intake, exercise, smoking cessation), bone mineral density (BMD) testing when appropriate, and adherence to medication when prescribed.

Nutrition: Ensuring Adequate Calcium and Vitamin D Intake

A crucial message to deliver to women of any age, especially those who are at increased risk for osteoporosis, is that healthy lifestyle choices and intake of appropriate amounts of critical vitamins and minerals can have a substantial impact on bone health at all stages of life. The three main factors are calcium consumption, vitamin D intake, and exercise (Tables 1, 2). Although inadequate calcium intake and vitamin D deficiency are common overall, women who may be at particular risk for calcium or vitamin D deficiency include those who frequently diet or avoid dairy products, older women with small appetites who consume a reduced number of calories, and women who have eating or medical disorders that interfere with nutrient absorption. Weight loss in elderly women, whether intentional or not, is associated with accelerated bone loss and an increased

risk of hip fracture.⁴ Ensuring adequate protein intake can help minimize bone loss among elderly women, and use of protein supplements by older women following hip fracture has been associated with significantly shorter hospital stays, improved clinical outcomes, and reduced rates of complications and mortality.⁴

The NOF advises that women older than age 50 take calcium supplements if needed to ensure that they consume at least 1,200 mg/d of elemental calcium.

Among its universal recommendations for all women, the NOF advises adequate calcium and vitamin D intake, lifelong participation in regular weight-bearing and muscle-strengthening exercise, avoidance of tobacco use, and identification and treatment of alcoholism.³ With advancing age, and especially after menopause, a woman's calcium requirements increase as intestinal absorption declines.⁴ Most US women consume too little dietary calcium—with a median intake of about

600 mg/d. Some women can consume sufficient calcium through dairy products such as milk, yogurt, or cheese, or through foods and juices fortified with added calcium. However, NOF advises that women older than age 50 take calcium supplements if needed to ensure consumption of at least 1,200 mg/d of elemental calcium.³ Most multivitamins include less than 500 mg of elemental calcium. Accordingly, most women will benefit from calcium supplementation in addition to their daily multivitamin.⁴ Although single doses of as much as 1,000 mg are acceptable, absorption improves when calcium is taken in smaller, divided doses. More than 1,200 to 1,500 mg/day of calcium offers minimal (if any) additional bone health benefits, and may increase the risk of kidney stones or cardiovascular disease.

TABLE 1. Calcium Content of Selected Foods

- Milk, whole or skim, 1 cup: 290-315 mg
- Yogurt, low-fat, 1 cup: 340-450 mg
- Sardines, 3 oz: 370 mg
- Collard greens, cooked, 1 cup: 300-350 mg

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TABLE 2. Sources of Vitamin D

- Exposure to sunlight (best source)
 - 5-15 min on arms and legs between 10 AM and 3 PM, 2-3 times/wk (women with darker skin need longer exposure)
 - Wearing sunscreen markedly reduces the skin's ability to produce vitamin D
- Vitamin D-fortified foods (milk/yogurt, some cereals/breads, some orange juice)
- Fatty fish
- Vitamin supplements (most common source)

Without adequate vitamin D intake, the body cannot absorb sufficient amounts of calcium from either dietary sources or supplements. The NOF recommends that women older than age 50 consume 800 to 1,000 IU/d of vitamin D₃, or an amount sufficient to achieve an average serum 25-hydroxy vitamin D concentration of at least 30 ng/mL.³ As with calcium, reliance on multivitamins alone is typically not sufficient for adequate vitamin D intake. Although supplements that contain only vitamin D are available, those that combine calcium and vitamin D may offer a more convenient dosing regimen.

Exercise and Fall Prevention

Perhaps one of the most important and challenging aspects of empowering patients to take action to improve their bone health and prevent osteoporosis is motivating them to exercise. It is clear that a sedentary lifestyle is associated with reduced bone mass, and that weight-bearing exercise stimulates new bone formation.¹ Activities such as aerobic exercise (eg, walking, jogging) and weight training, which increase muscle mass and improve strength, apply substantial stress to bone and stimulate the body to increase bone mass.⁴

Women need to understand that daily exercise, or exercising for long stretches of time or at high intensity, is not necessary to derive bone health benefits. Likewise, the benefits of physical activity can be reaped without access to expensive exercise equipment, exercise classes, or personal training sessions. A position statement from NAMS notes that strength training performed twice a week can be effective in maintaining bone health.⁴

ACOG advises that repeat BMD screening be performed every 2 years.

Fall prevention should be emphasized as part of a fracture prevention strategy (Table 3). When recommending exercise to elderly women with established osteoporosis, it is important to emphasize that even moderate physical activity can contribute to a reduced risk of falls and fall-related injury by enhancing muscle strength, agility, and balance.⁴ However, women with osteoporosis should be cautioned against rigorous or heavy weight-bearing exercise that could actually cause fracture.⁴

BMD Follow-up: Misconceptions and Pitfalls

Unlike yearly mammography to screen for breast cancer, BMD testing is neither necessary nor cost-effective on an annual basis. Following an accelerated loss of BMD in early postmenopause, on average postmenopausal women lose 1% to 1.5% of their bone mass each year.⁴ In the absence of new risk factors, ACOG advises that repeat BMD screening be performed every 2 years.¹ Overall, follow-up screening has the greatest value for:

- Older women
- Patients with low baseline BMD values
- Women with a greater number of risk factors.¹

Follow-up assessment of BMD with dual-energy x-ray absorptiometry (DEXA) when monitoring women receiving therapy for established osteoporosis presents its own unique challenges, as it might not yield clinically useful information until the patient has completed 2 years of treatment.⁴ Women should be cautioned against unrealistic expectations of measurable gains in BMD early in the course of treatment.

Indeed, DEXA tests are fraught with intrinsic variability. Follow-up DEXA assessments are often performed by a different technician using a different machine. Individual technicians may vary in their testing technique, and these differences—combined with the possibility of positioning errors on DEXA scanning—may introduce variability into the assessment process. Even with proper quality assurance procedures in place, two machines may have subtle differences in precision and degree of variance. As a result, it can be difficult to draw conclusions directly from the comparison of serial BMD tests.

Statistically insignificant reductions in BMD among women receiving treatment for osteoporosis are likely artifacts of the imprecision of DEXA scanning.⁴

However, if a statistically significant decline (more than 4% to 5%) occurs, further evaluation may be warranted to search for alternative causes of bone loss and assess patients' adherence to therapy.⁴

Where Do Estrogen and Progestin Fit?

Does estrogen alone or estrogen combined with progestin therapy have a role in the prevention or treatment of osteoporosis? Initial study results from the Women's Health Initiative (WHI) demonstrated a significant decrease in fracture risk among healthy women using hormone therapy (HT): a 34% reduction in hip and vertebral fractures and an overall 24% reduced fracture risk with the use of conjugated equine estrogens (0.625 mg/d) with medroxyprogesterone acetate (2.5 mg/d).⁵ Even lower doses of these two agents may prevent bone loss and improve BMD.

Hormone therapy appears to offer maximal benefit for younger women who are less than 10 years postmenopausal, although substantial improvement in BMD has been demonstrated with HT among older women as well.¹ Discontinuation of HT has been shown to result in increased bone turnover and accelerated bone loss.¹ Nonetheless, as the WHI also linked HT with increased risks of cardiovascular disease in older menopausal women and breast cancer with more than 5 years of use of combination estrogen-

progestin HT, the decision on whether to use it must be individualized after reviewing risks and benefits with the patient.

Pharmacologic Treatment Counseling

Although a combination of calcium, vitamin D, and exercise is the cornerstone of any osteoporosis prevention and treatment strategy, women at increased risk for fracture—including those with established osteoporosis—should receive pharmacologic therapy. When selecting from among the many options for the drug class that would be most appropriate for an individual patient, crucial considerations are adherence and identifying key factors that affect adherence, including side effects, mode of administration, and dosing regimen.

In discussing treatment options with patients, clinicians should ask questions about lifestyle and preferences that will help them identify which women are more likely to remember to take a daily medication, for example, and which might benefit from a regimen that

It is appropriate to inquire whether patients can see themselves successfully using weekly or monthly oral regimens, or less frequent administration via the intravenous (IV) route.

requires less frequent dosing. Regarding bone-specific therapies for fracture prevention, it is appropriate to inquire whether patients can see themselves successfully using weekly or monthly oral regimens, or less frequent administration via the intravenous (IV) route.

Adherence Issues

Adherence to oral osteoporosis therapy is poor overall.⁴ A study of more than 10,500 women intended to evaluate adherence and persistence associated with use of the oral bisphosphonate drugs alendronate (Fosamax) and risedronate (Actonel) and the selective estrogen receptor modulator raloxifene (Evista) reported suboptimal adherence and persistence rates regardless of patient age or dosing regimen.⁶ In general, adherence rates ranged from 54% to 61%.

Persistence, defined as continuous use of the same drug over a 12-month period, was similar for all 3 medications, characterized by a sharp decline during the first 3 months, with a subsequent slower but continued decline throughout the study period. At 12 months, persistence rates ranged from 16% to 21%.⁵

The AHRQ identifies three main barriers to adherence and persistence: mode of administration, dosing regimen, and cost.² Bisphosphonates can be delivered orally or intravenously; oral bisphosphonates must be taken on an empty stomach first thing in the morning

TABLE 3. Basic Fall Prevention

- Exercise to improve balance and muscle strength
- Alcohol avoidance
- Modification of physical environment
- Ample lighting
- Removal of ambulatory obstacles (eg, no clutter on floor, clear hallways, no furniture in pathway)
- Nonskid rugs and carpets
- Tub and shower safety (grab bars, nonskid floors)
- Safe stairs (handrails, good condition, nonslip)

with 8 ounces of plain water, with no additional food or drink consumption for at least 30 minutes and the patient remaining upright during this time. Dosing regimens for the bisphosphonate drug class vary from daily to weekly, twice a month or monthly, or once every 3 months for IV ibandronate (Boniva) and once a year for IV zoledronic acid (Reclast).

The oral bisphosphonates share a common risk profile in terms of their potential to cause gastrointestinal (GI) problems, including difficulty swallowing, gastroesophageal reflux, inflammation of the esophagus, and gastric ulcer. Patients prescribed oral bisphosphonates should be counseled that deviating from dosing instructions increases the likelihood of experiencing GI concerns. However, even when complete and clear instructions are provided, between 25% and 50% of patients will disregard at least one component of the protocol.⁶ For example, not following the instruction to take the medication with only plain water can substantially reduce bisphosphonate absorption; substituting coffee or juice for water can reduce drug absorption by as much as 60%.⁷

Intravenous delivery of a bisphosphonate such as ibandronate or zoledronic acid is not associated with GI difficulties. More importantly, IV treatment eliminates the concern over incorrect or inconsistent administration by the patient.

Conclusion

Maintaining bone health and preventing osteoporosis and osteoporotic fractures require a multifaceted approach that incorporates lifestyle issues, nutritional

supplementation, BMD testing, and (when indicated) pharmacologic intervention. Because of their regular, continuing contact with their patients, ObGyns who remain up to date and interested in the lifestyle, diagnostic, and pharmacologic measures reviewed in this newsletter are in a unique position to help their patients achieve the goal of bone health.

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