



IMPROVING OSTEOPOROSIS OUTCOMES in Primary Care

Learning Objectives

After completing this activity, participants should be better able to:

- Identify patients at risk for osteoporosis utilizing available assessment tools
- Outline the relative merits and drawbacks of pharmacotherapeutic approaches for osteoporosis
- Implement strategies to improve clinical care of patients with osteoporosis that are related to compliance, adverse effects, and treatment failure

Osteoporosis Risk Factors

As bone mass is lost, trabeculae—the horizontal connecting struts within healthy bone—become perforated and disconnected. This leads to a vertebral fracture, resulting in changes in body configuration—loss of height, kyphosis—and back pain. The National Institutes of Health defines osteoporosis as a disease of bone strength.¹ The tool currently used to diagnose osteoporosis, bone densitometry, only measures the amount of calcium in the skeleton. It doesn't measure the architectural changes that occur.

The most predominant risk factor for osteoporosis is low bone mass, which by itself predicts fracture risk. Unfortunately, many unmodifiable attributes are risk factors for osteoporosis as well, such as aging, history of fracture in a first-degree relative, and race.² There are also many lifestyle factors that have an impact on bone mass, most commonly low calcium intake and vitamin D deficiency (Table 1).^{1,2} These are factors that can be modified and discussed with patients in daily practice.

Osteoporosis has a number of secondary causes as well, such as rheumatic and autoimmune diseases, hypogonadal states, liver diseases, endocrine disorders, and gastrointestinal (GI) disorders.² Celiac disease, which compromises absorption

Osteoporosis treatment is based on a careful risk-benefit analysis that includes comprehensive assessment and clinical judgment as well as patient preference.

**Does compliance with treatment impact the rate of fracture?
See page 46**

Table 1. Risk Factors for Osteoporotic Fracture

Biological risk factors

- Low bone mass
- Advancing age
- Personal history of osteoporosis or fracture as an adult
- History of fracture in a close relative (especially parents)
- Certain medications, eg, use of glucocorticoid therapy for ≥ 3 months
- Being a Caucasian or Asian postmenopausal woman
- Small, thin frame
- Hypogonadism
 - Premature estrogen deficiency in women <45 years of age
 - Low testosterone levels in men

Lifestyle risk factors

- Low calcium intake
- Vitamin D insufficiency
- High salt, cola, or caffeine intake
- Immobilization
- Alcohol (≥ 3 drinks/day)
- Inadequate physical activity
- Low body mass index
- Smoking (active or passive)

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of nutrients from the gut, is highly prevalent in patients with osteoporosis and is often missed because it is commonly asymptomatic. In fact, patients who present with osteoporosis at an age younger than might be expected (women, age 55 years; men, age 60 years) should be screened for celiac disease. A thorough history and physical examination may identify secondary causes of osteoporosis since many of these conditions will be present and cause symptoms prior to a diagnosis of osteoporosis.

Assessing Risk of Osteoporosis

The National Osteoporosis Foundation's *Clinician's Guide to Prevention and Treatment of Osteoporosis* outlines recommendations for bone mineral density (BMD) testing.² Patients who may need treatment for osteoporosis and who have had a fracture after age 50 are candidates for BMD testing. It is important to note that perimenopausal and postmenopausal fractures may be osteoporosis-related and that some women go through menopause at a younger age. Patients receiving treatment for osteoporosis should have regular BMD testing to monitor therapeutic effects. BMD should be conducted in anyone not receiving therapy in whom evidence of bone loss would lead to treatment, and, as demonstrated by results of the Women's Health Initiative,³ women who stop estrogen therapy should receive BMD testing since rapid bone loss occurs after estrogen is discontinued.

The World Health Organization (WHO) definitions of osteoporosis include normal bone mass, which is a T-score above -1 ; low bone mass, which is a T-score between -1.0

and -2.5 ; and osteoporosis, which is a T-score below -2.5 (Figure 1).⁴

A thorough personal and family history and physical examination are required to assess people older than 50 who might be at risk for osteoporosis. Inquiry into dietary habits and preferences is also important to ensure that the patient's diet does not pose an added risk factor.

When appropriate, consider BMD testing. Women should have a bone density test by the age of 65 years and men by the age of 70 years.² To examine possible secondary causes, assessment may include laboratory tests as indicated by the history and physical examination. For example, 25-hydroxy-vitamin D (25[OH]D) can be measured to determine whether sufficient levels are present. In patients with a low hip bone to spine bone density ratio, asymptomatic primary hyperparathyroidism should be investigated since these patients tend to have lower cortical bone mass than trabecular bone mass and the hip has more cortical bone than the spine. Finally, FRAX[®] should be used to assess fracture risk and determine whether intervention is necessary.

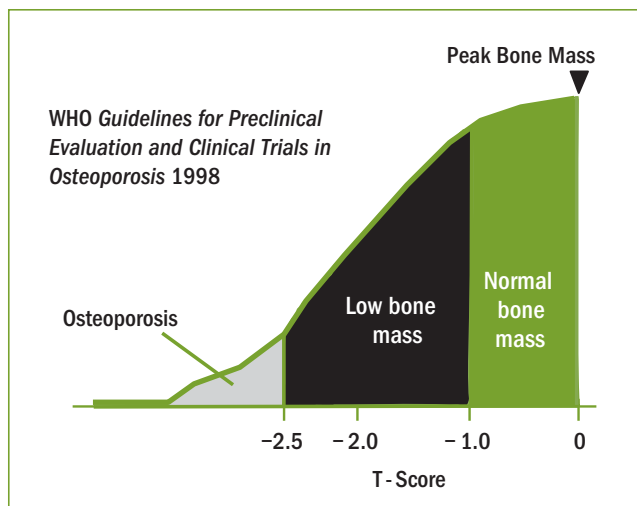


Figure 1. WHO osteoporosis guidelines. National Osteoporosis Foundation²; World Health Organization.⁴ ©2009. National Osteoporosis Foundation. All rights reserved. www.nof.org.

FRAX[®] (www.shef.ac.uk/FRAX/) is a Web-based risk assessment tool developed by the WHO that assesses a patient's 10-year fracture risk. FRAX[®] predicts 10-year hip fracture risk and the 10-year probability of major osteoporotic fractures (clinical spine, forearm, hip, or shoulder fracture). FRAX[®] risk models are based on studies of population-based cohorts from Europe, North America, Asia, and Australia.

FRAX[®] can be used for postmenopausal women and men older than 40 years; the algorithm does not work for persons younger than 40. FRAX[®] should only be used in treatment-naïve patients, and in the United States, only in patients with low bone mass. FRAX[®] is not appropriate for use in patients who already have osteoporosis or patients who have had a hip or clinical spine fracture because they are already high risk and require treatment. FRAX[®] is also not appropriate for people with a T-score above -1 because their risk is sufficiently low.

To calculate an individual risk score, the online FRAX[®] Calculation Tool prompts users to select from a menu of countries and, for the United States, to select among 4 racial or ethnic options. The questionnaire screen lists 12 risk factors for osteoporosis⁵ (Figure 2), requiring a numerical value or “yes” or “no” response as appropriate. Incorrect entries may lead to wrong conclusions that may affect treatment decisions.

Approaches to Treatment

The treatment decision-making process is based on a risk–benefit analysis that includes clinical

FRAX[®] Calculation Tool Risk Factors

- | | |
|-------------------------|---|
| 1. Age | 8. Glucocorticoids |
| 2. Sex | 9. Rheumatoid arthritis |
| 3. Weight (kg) | 10. Secondary osteoporosis |
| 4. Height (cm) | 11. Alcohol 3 or more units per day |
| 5. Previous fracture | 12. Femoral neck BMD (g/cm ²) |
| 6. Parent fractured hip | |
| 7. Current smoking | |

Figure 2. FRAX[®] Calculation Tool risk factors. Clinical risk factors require a “yes” or “no” response. A “no” response is the default if an option is not selected. Available at: www.shef.ac.uk/FRAX.

assessment, bone density, results of a diagnostic workup, risk of fracture (eg, as assessed by FRAX[®]), and clinical judgment. Discussions with the patient may determine that although there is an increased risk of fracture, the possibility of and concern about adverse effects of pharmacotherapy might be considered too high.

If a patient’s T-score is lower than -1 , the next

step is to ensure adequate calcium and vitamin D intake and perform BMD testing 3 to 5 years later. If the patient is elderly, it is also important to ensure reasonable protein intake. Adequate physical activity is an essential element of managing bone health. The activity should be something an individual enjoys doing to ensure that they “stick with it,” and it can be helpful to exercise with a friend for encouragement. The type of activity does not matter as much as the consistence as long as the individual chooses weight-bearing or muscle-strengthening exercises. Advising individuals to do balance training exercises such as tai chi is also important for preventing falls.

In postmenopausal women and men older than 50, risks for falls should be addressed, including recommendations for regular exercise that includes weight-bearing activity or muscle strengthening 2 to 3 times a week.² Risk factors for low bone mass should be addressed and recommendations made to ensure adequate calcium and vitamin D intake and, for the elderly, adequate protein intake. All at-risk patients should avoid tobacco and excessive use of alcohol.

The average adult aged ≥ 50 years needs 800 International Units (IU) to 1000 IU of vitamin D daily.⁶ For patients younger than 50 years, 400 IU to 800 IU of vitamin D daily is sufficient. Supplementation is advisable for most people, particularly those with chronic illness, housebound patients, and others with limited sun exposure. Vitamin D is synthesized in the skin and any of the agents used for sunburn protection will reduce this natural ability. The capability for producing vitamin D in the skin also decreases with age.

The National Osteoporosis Foundation recommends initiating therapy to reduce fracture risk if a patient has a hip fracture or a spine fracture.² This includes both clinical and subclinical fractures, such as a patient with back pain or a fracture discovered on an x-ray or via lateral vertebral assessment, which would use DXA scan data. Treatment should also be implemented in patients with a T-score -2.5 or less or between -1.0 and -2.5 and who have a 10-year

probability based on US-adapted FRAX[®] of hip fracture $\geq 3\%$ or if there is a 10-year probability of any major osteoporosis-related fracture $\geq 20\%$ (Table 2). Because fracture risk varies by country, entering a country other than the United States into FRAX[®] will produce a totally different risk assessment.

Pharmacotherapy

There are currently a number of US Food and Drug Administration (FDA)–approved options for osteoporosis treatment. The antiresorptive agents are also called anticatabolic agents. Principal among them are the bisphosphonates, which allow for multiple routes and schedules of administration. Other options include calcitonin, an estrogen agonist/antagonist (EAA) formerly termed a selective estrogen receptor modulator, and hormone therapy. There is also one anabolic agent that actually helps the body form bone (Table 3).

Bisphosphonates

The bisphosphonates alendronate, ibandronate, risedronate, and zoledronic acid are all approved for the prevention and treatment of postmenopausal osteoporosis. Alendronate, risedronate, and zoledronic acid are also approved for the treatment of glucocorticoid-induced osteoporosis in men and women. Additionally, zoledronic acid is approved to prevent the recurrence of fracture in patients who have had a hip fracture and to prevent and treat glucocorticoid-induced osteoporosis in men and women. This is the only agent with this indication for prevention, and normal renal function must be confirmed before it is used. Serum calcium and 25(OH)D must also be normal to reduce the risk of hypocalcemia. Bisphosphonate regimens and indications are listed in Table 4.

Clinical trials of bisphosphonates found that all reduced vertebral fractures, but results varied with nonvertebral fractures. The Fracture Intervention Trial (FIT) showed a reduction in vertebral fractures and a reduction in any clinical fracture with alendronate, but less benefit in patients who did not have a prior fracture.⁷ There was also a much smaller benefit in patients with nonvertebral fracture. Consequently, alendronate's indication is for prevention of the risk

Table 2. National Osteoporosis Foundation Recommendations for Initiation of Therapy

Initiate therapy to reduce fracture risk in postmenopausal women and men age 50 and older if:

- The patient has a hip or vertebral (clinical or morphometric) fracture
- T-score is ≤ -2.5 after evaluation to exclude secondary causes
- T-score is between -1.0 and -2.5 and 10-year probability of hip fracture is $\geq 3\%$ or there is a 10-year probability of any major osteoporosis-related fracture $\geq 20\%$ based on US-adapted FRAX[®]

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Table 3. FDA-Approved Options

**Antiresorptives/anticatabolics
(bone-retaining) Agents**

- Bisphosphonates
 - Alendronate (oral)
 - Risedronate (oral)
 - Ibandronate (oral or IV)
 - Zoledronic acid (IV)
- Calcitonin
- Estrogen agonist/antagonist (EAA)
 - Raloxifene
- Estrogen/hormone therapy

Anabolic (bone-forming) Agents

- Teriparatide (rhPTH [1-34])

IV = intravenous.

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of spine fractures and hip fractures only and not for prevention of all fractures.

The Vertebral Efficacy With Risedronate Therapy (VERT) trial showed a reduction in both vertebral and nonvertebral fractures with risedronate.⁸ Ibandronate reduces the risk of vertebral fractures, although there is no prospective evidence that ibandronate reduces the risk of nonvertebral fractures. Data for zoledronic acid show a fairly large reduction in nonvertebral fractures, a 70% reduction in morphometric fractures, a reduction in hip fractures, and a reduction in any clinical fractures.⁹

It is important to note that there are no head-to-head studies of bisphosphonates. These are independent studies, and observed reductions may be related to the study population rather than the potency of the drug. Thus these agents cannot be rank ordered based solely on safety and efficacy profiles.

Bisphosphonate Adverse Events

Esophageal irritation, including heartburn, nausea, and reflux symptoms, is common

with a daily bisphosphonate dosing regimen. Although adverse events are less common with the once-weekly dose, they still occur.

Zoledronic acid, which is given intravenously once a year or once every 2 years, may cause an acute-phase response. After the first dose patients may experience flu-like symptoms for a day or two. Zoledronic acid causes the immune system to release cytokines that mimic the flu and produce fever, muscle pains, and aches. Acetaminophen relieves the symptoms.

The FDA has issued a letter warning about bone and muscle pain following treatment with bisphosphonates, noting that this can occasionally be intractable. If it occurs, it usually does within the first 3 or 4 months. If a patient is taking an oral bisphosphonate, these symptoms stop with the cessation of the bisphosphonate; patients can usually restart the bisphosphonate without recurrence. This cannot be done with an intravenous bisphosphonate, which is one of the disadvantages of the administration route.

There have also been reports of an increased risk of atrial fibrillation with all bisphosphonates. Multiple studies of the class have produced mixed results and the issue is currently under FDA review.

Osteonecrosis of the jaw, while it has been associated with bisphosphonate use, is extremely

rare and is a very unusual phenomenon in people taking these drugs for osteoporosis.¹⁰ It can be a problem in cancer patients receiving high doses of intravenous bisphosphonate. It is important to note that these patients are receiving other chemotherapeutic agents, are immunocompromised, and often have poor oral hygiene. Poor oral hygiene and smoking are risks for osteonecrosis in the general population. Part of the problem with reaching a better understanding of the osteonecrosis population is that the background rate of osteonecrosis is not known.

There have been reports of esophageal cancer in patients taking alendronate. Esophageal cancer is actually unusual in people who take alendronate compared with data from the National Cancer Institute. All oral bisphosphonates are contraindicated in patients with pre-existing esophageal lesions such as Barrett's esophagitis.

Calcitonin

Calcitonin is approved by the FDA for treatment of osteoporosis in women at least 5 years postmenopausal and is not considered first-line monotherapy. It is available as a 200 IU daily nasal spray or by injection (various dosages). Although there was a significant reduction in new vertebral fractures at the 200-unit dose (33% compared with placebo), there was no difference at the 400- or 100-unit doses.¹¹ Adverse effects of the calcitonin nasal spray include rhinitis and occasional nasal bleeding. It may worsen nasal symptoms in patients with allergies.

Estrogen Agonist/Antagonist (EAA)

Raloxifene is the only EAA available. While it is not an estrogen, it works through the estrogen receptor and has estrogen agonist effects on bone. In controlled trials, raloxifene prevented bone loss in the spine and reduced the risk of vertebral fractures, but, over an 8-year period, the drug has not been shown to reduce the risk of nonvertebral fractures.¹² It has been shown

Table 4. Bisphosphonates: Regimens and Indications

Generic Name	Route		PMO		GIO		Men
	Oral	IV	Prevention	Treatment	Prevention	Treatment	
Alendronate	Daily, Weekly		X	X		X	X
Risedronate	Daily, Weekly, Monthly		X	X	X	X	X
Ibandronate	Daily, Monthly	Quarterly	X	X			
Zoledronic acid		Yearly, Biyearly	X	X	X	X	X

PMO = postmenopausal osteoporosis; GIO = glucocorticoid-induced osteoporosis.

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to reduce the risk of estrogen receptor–positive breast cancer and is indicated for breast cancer risk reduction in women between the ages of 50 and 60 who do not have menopausal symptoms and who are at risk for breast cancer.

Raloxifene is an estrogen antagonist in the central nervous system and so adverse effects include mild menopausal symptoms such as hot flashes. Mild leg cramps and fluid retention may occur due to the drug's estrogen agonist activity in the peripheral vasculature. Deep vein thrombosis has been reported (hazard ratio, 2.4; 95% confidence interval, 1.2–4.5)¹³ and a single study showed a slight increase in the risk of fatal stroke (absolute risk increase, 0.7 per 1000 woman-years).¹⁴

Estrogen/Hormone Therapy

The Women's Health Initiative, despite the study's drawbacks, demonstrated that estrogens do reduce fracture risk. There was a 34% reduction in hip fracture risk, 34% reduction in clinical vertebral fractures, and 23% reduction in other osteoporosis-related fractures. However, in the combination therapy arm, which used estrogen plus progestin, there was an increase in heart attack, blood clots, and stroke. The average age of study participants was 62 years and the majority of women were postmenopausal.³

FDA recommendations for the use of estrogen to prevent osteoporosis state the following¹⁵:

- All nonestrogen preparations should be considered first
- When estrogen/hormone therapy is prescribed, it should be in the smallest dose for the shortest time required to achieve treatment goals
- Prescribe estrogen/hormone therapy products only when the benefits are believed to outweigh risks for an individual patient

A longitudinal study of menopausal symptoms showed that, on average, symptoms last 4 to 5 years, so some women may require estrogen for a longer period of time. For conjugated estrogens, which are the usual oral estrogens, 0.3 mg is usually an adequate dose. This is double the dose used in the Women's Health Initiative.

Anabolics

Teriparatide, a recombinant form of parathyroid hormone, is the only treatment for osteoporosis that builds bone. It reduces the risk of both vertebral and nonvertebral fractures and increases vertebral, femoral, and total body BMD. However, it does have drawbacks: It is very expensive, it requires a daily injection, and because long-term effects are unknown and earlier animal studies showed an increase of osteosarcoma, the FDA currently limits use of teriparatide to a maximum of 2 years. At the end of 2 years some clinicians recommend starting a bisphosphonate, although this is not mentioned in labeling for teriparatide; however, once teriparatide is terminated, patients will begin to lose bone again. Side effects with teriparatide in clinical trials were mild and included leg cramps, dizziness, and arthralgias. Transient hypercalcemia may occur; if the patient injects the drug in the morning and 3 hours later goes for a blood test, calcium levels are likely to be high but will normalize by the next morning.

Combination Therapy

Combination therapy is generally not recommended, but candidates include patients taking antiresorptive treatment for 2 years who have continued bone loss after treatment, fractures during or after treatment, and persistent low BMD. For these patients, combination therapy with a bisphosphonate and teriparatide can be considered. Antiresorptive agents are never used together. Before initiating combination therapy, celiac disease and other secondary causes of osteoporosis should be ruled out. The most common reasons

women do not respond to bisphosphonate therapy are noncompliance and lack of persistence or failure to absorb the drug. Absorption characteristics of oral bisphosphonates tend to be erratic in general, with only 0.7% of a tablet absorbed under the best physiologic circumstances. It doesn't take much alteration in the function of the GI tract to reduce or eliminate absorption completely. The impact of combination therapy on fracture rates is also unknown.

Novel and Emerging Therapies

A number of new EAAs are currently in development. Bazedoxifene is in preapproval stage with the FDA, as is a combination of bazedoxifene and a conjugated estrogen, with the bazedoxifene used as a progestin. Arzoxifene is currently in phase 3 development trials.

Denosumab, a human antibody, is a RANK ligand inhibitor taken twice a year as a subcutaneous injection. It is currently under review by the FDA. Two other therapeutic options are 1 or 2 years farther out—the cathepsin K inhibitor, odanacatib, is in early phase 3 trials, as is parathyroid hormone analog ostabolin-C.

Long-term Approaches to Osteoporosis

Women who are postmenopausal and men 50 years and older should have an annual clinical evaluation. Those who are not on medical therapy should be re-evaluated for osteoporosis fracture risk. Patients who are being treated for osteoporosis should also be reevaluated. BMD

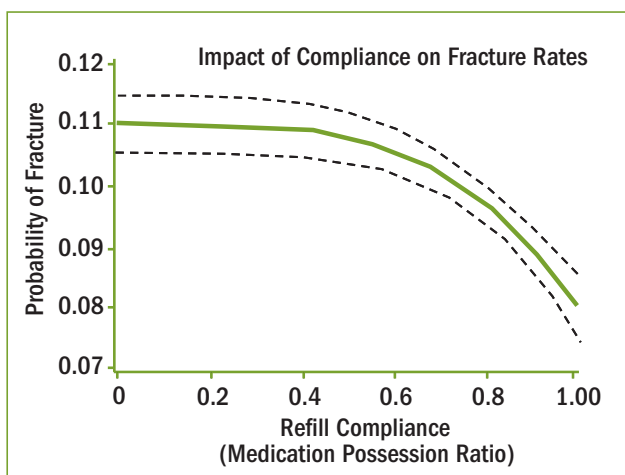


Figure 3. There is a significant, progressive relationship between refill compliance and fracture risk reduction. Differences in fracture rates were seen at 50% compliance with further decreases observed at 75% compliance. Reprinted with permission from Siris ES, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clin Proc.* 2006;81:1013-1022. Dowden Health Media.¹⁶

testing should be repeated after being on bisphosphonates for a year and then every 1 to 2 years as long as they are on medication and at 1- to 5-year intervals depending on initial risk.² Medicare allows one BMD test after initiating therapy. Thereafter, BMD testing should be done every couple of years.

It is unclear how long treatment should continue. The bisphosphonates have the unique ability to accumulate in the skeleton. But limited long-term data suggest that decisions on treatment duration should be made on a case-by-case basis and guided by individual reevaluation of clinical fracture risks, BMD, and safety and efficacy issues. In patients with high fracture risk after 5 years of treatment with bisphosphonates, continuation could be considered. If fracture risk is low, discontinuation may be appropriate. The usefulness of more than 5 years of treatment will need to be proved with higher levels of evidence-based medicine.

For treatment across a patient's lifespan, different agents have different benefits and risks for each age group. An intravenous bisphosphonate may be best in an older patient, an oral bisphosphonate in a younger patient, and raloxifene in early postmenopause. Patients should be reassessed every year. Adverse events should be discussed, and patients should be queried on what they think about the medication and how they are feeling. Osteoporosis therapy should be considered temporary and not as chronic lifetime treatment. Drug holidays may be appropriate in some patients, but they should still be carefully monitored and followed during the drug-free period. Follow-up after discontinuation should include BMD testing and assessment of markers of bone metabolism.

Improving Patient Compliance and Persistence

Half of patients prescribed medication for osteoporosis will stop taking it at the end of the first year, a rate similar to patients who are taking blood pressure and cholesterol medications.¹⁷ Extended gaps in treatment are common. Osteoporosis is an asymptomatic disease, so if a patient takes the medication and experiences adverse effects and stops, bone density declines with no overt evidence until a fracture occurs.

Adverse events and the perception that the medication is not effective are the main factors leading to noncompliance, since bone density often will not change. If bone density declines, it has to drop more than 3% or 4% before it is out of the range of error of the test. An inconvenient dosing regimen can also cause noncompliance. Oral bisphosphonates have to be taken first thing in the morning with water on an empty stomach. Patients then have to wait half an hour to an hour before eating or drinking, and it is necessary to remain sitting up or standing during this time. Cost is less of an issue now that generic alendronate is available.

Compliance with an osteoporosis medication regimen impacts the rate of fracture (Figure 3).¹⁶ It is necessary to take at least 80% of the prescribed regimen to see a drug benefit, which is calculated as reduction in the probability of fractures.¹⁶ Benefit begins to decline at and below 80%.

Compliance can be improved by changing the drug and simplifying the dosing regimen. Different people will prefer different regimens and that may be all that is required. Patients respond to being informed with education on osteoporosis and its treatment. Telephone

counseling or referral to local support groups can also help by keeping them involved with their care. A simple follow-up phone call from the clinician a month after therapy is initiated can make the patient feel that the healthcare provider is interested in the patient's well-being and in treatment success. Patient monitoring by nursing staff has significantly increased cumulative compliance with treatment. Each of the methods can help keep the patient attuned to the importance of compliance and persistence.

Patients With a History of Fracture Do Not Receive Treatment

On average, fewer than 20% of people who have a hip fracture are treated for osteoporosis. Recently, the National Committee for Quality Assurance (NCQA) found that only 20.4% of patients with any fracture after the age of 67 were being managed.¹⁸ According to the Health Effectiveness Data and Information Set (HEDIS) criteria established by NCQA to measure health plan performance, every person older than 65 who has a fracture should receive a diagnostic workup or treatment for osteoporosis. Anyone who has a hip fracture has osteoporosis by definition.

Nationally, improving clinician awareness of the importance of timely assessment and treatment of osteoporosis is a challenge. Change needs to come from within the system, and clinicians today, no matter what the practice setting, must realize they are not working in a vacuum—that they are, typically, one of a group of healthcare professionals who care for an individual patient. In family medicine, if a patient presents with a history of fracture in the past year, discuss the circumstances and note details in the chart. If the fracture was the result of a car accident, the clinician needs to look beyond the incident itself; there is probably underlying pathology that needs to be addressed and requires patient referral. Any clinician can begin the referral process. It is extremely important for every clinician to behave like a part of a “whole patient” practice team. If the index of suspicion is high, action should be taken.

Read Q&A from the live symposia at www.practicingclinicians.com/H2_2009/osteoqa.pdf

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