Emerging Approaches in Managing Postmenopausal Osteoporosis

Introduction

Identifying and Reaching Patients With Postmenopausal Osteoporosis: Where Should We Look? How Should We Test?
Ethel Siris, MD
Madeline C. Stabile Professor of Clinical Medicine
Columbia University College of Physicians and Surgeons
Director, Toni Stabile Osteoporosis Center
Columbia University Medical Center
New York, NY

Osteoporosis Treatment: Defining Goals, Optimizing Strategies
E. Michael Lewiecki, MD, FACP, FACE
Clinical Assistant Professor of Medicine
University of New Mexico School of Medicine
Osteoporosis Director
New Mexico Clinical Research & Osteoporosis Center
Albuquerque, NM

New Pathways in Osteoporosis Therapy: A Preview of New Agents
Steven R. Cummings, MD, FACP
Professor of Medicine and Epidemiology
Women’s Health Clinical Research Center
University of California at San Francisco
San Francisco, CA

Post-Test / Evaluation Form

Release Date of Activity: September 2010
Expiration Date of Activity for AMA PRA Credit: September 30, 2012
Estimated Time to Complete This Activity: 1.5 hours
Emerging Approaches in Managing Postmenopausal Osteoporosis

EDUCATIONAL NEEDS

The appropriate and successful management and treatment of patients at risk for postmenopausal osteoporosis or who have the condition depends on effective and accurate assessment of symptoms early in the disease. All health care professionals should be aware of the signs and symptoms of osteoporosis and should be able to perform a risk assessment in postmenopausal patients. Evaluation involving the FRAX® algorithm (an assessment tool developed by the World Health Organization) is particularly suited to the primary care practice. Clinicians also should be prepared to refer patients for radiologic testing with dual-energy X-ray absorptiometry when appropriate. In addition, the institution of pharmacologic therapy, when indicated, is well within the purview of primary care clinicians who are familiar with the available agents and are comfortable prescribing them. This educational activity provides needed information regarding the identification, diagnosis, and treatment of osteoporosis—or increased risk for this condition—in postmenopausal patients.

LEARNING OBJECTIVES

After reading and studying this supplement, participants should be able to:

• Describe the etiology of postmenopausal osteoporosis and explain the importance of disease and fracture prevention.
• Relate the reasons why postmenopausal osteoporosis is not adequately recognized and treated, particularly in certain populations.
• Discuss measures that could be taken to improve adherence to treatment.
• Explain how the World Health Organization’s FRAX algorithm and dual-energy X-ray absorptiometry can be used in primary care practice to identify patients who are at risk for osteoporosis and who may be candidates for pharmacologic intervention for prevention and/or treatment.
• Identify pharmacologic agents that are currently available to prevent and treat postmenopausal osteoporosis and describe their benefits and limitations.
• List and describe the newer agents for the treatment of osteoporosis that currently are in clinical trials.

DISCLOSURE

Dr Cummings has been a consultant and speaker for Amgen and Eli Lilly. Dr Lewiecki, during the past year, has owned personal investments in the following companies or received grant/research support (principal investigator, funding to New Mexico Clinical Research & Osteoporosis Center) from Amgen, Eli Lilly, Genentech, Merck, Novartis, and Warner Chilcott. He is on the scientific advisory board and speakers’ bureau of Eli Lilly, Genentech, and Novartis. Dr Siris has been a consultant and speaker for Amgen and Eli Lilly. She has also been a consultant for Novartis and sanofi-aventis.

CHSE Committee Members have no relevant financial relationships with any commercial interests: Carolyn Burns, MD; Dedra DeBerry, MA; Joyce Dunagan, MA, MSLS; Linda H. Freeman, DNS, RN; Paul Fultz; Terri Gipson, MSL; Ruth Greenberg, PhD; Lucy Juett, MS; Irene Litvan, MD; Loretta Malandra; Mike Mansfield, DMD; Ashlee Melendez, RN, BSN; Lisa J. Pfister, MD; Robert Sexton, MD; Uldis Streips, PhD; Kathy M. Vincent, MD; Lori Wagner, MD; Stephen Wheeler, MD; and Sharon Whitmer, EdD.

CME Reviewer: Shirley Jones, Sylvia Reitman, and Michelle Rizzo with Global Academy for Medical Education have no relevant relationships with any commercial interests.

RESOLUTION OF CONFLICT OF INTEREST

The CHSE has implemented a process to resolve conflict of interest for each CME activity. In order to help ensure content objectivity, independence, and fair balance and to ensure that the content is aligned with the interest of the public, the CHSE has resolved the conflict by external content review.

UNAPPROVED/OFF-LABEL USE DISCLOSURE

The CHSE requires CME faculty to disclose to the participants:

1. When products or procedures being discussed are off-label, unlabeled, experimental, and/or investigational (not US Food and Drug Administration [FDA] approved); and
2. Any limitations on the information that is presented, such as data that are preliminary or that represent ongoing research, interim analyses, and/or unsupported opinion.

Faculty may discuss information about pharmacological agents that are outside of FDA-approved labeling. This information is intended solely for CME and is not intended to promote off-label use of these medications. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

None of the authors discusses off-label uses of any FDA-approved drugs.

In his article, Dr Cummings discusses lasoxifene, which is approved in Europe but not in the United States, and arzoxifene, which will not be considered for approval by the FDA. In addition, Dr Cummings discusses the mechanisms of action of and potential uses for several novel osteoporosis treatments currently in phase II or phase III clinical trials: anticortisol antibody, bazoxifene, bazoxifene/conjugated estrogen combination, and odanacatib.

METHOD OF PARTICIPATION

To get instant CME credit online, go to http://louisville.edu/hsc/continuinged/earn-ce-credits/osteo. Type the above address into your address bar in Internet Explorer. If you are unfamiliar with what an address bar is or how to access yours, open Internet Explorer, then hold down the control key and press the “O” key on your keyboard. A dialogue box will open—this is where you will type the above address. After you have typed the address, click OK to go to the evaluation. Upon successful completion of the online test and evaluation form, you’ll be directed to a Web page that will allow you to receive your certificate of credit via e-mail. Please add chse@louisville.edu to your e-mail “safe” list. Once you have completed the evaluation, it will give you a password. Please be sure to write it down; you will then be able to access your certificate. Please note, certificates will not be mailed, so be sure to print a copy for your records.

If you have any questions or difficulties, please contact the University of Louisville School of Medicine Continuing Health Sciences Education office at (502) 852-5329.
Osteoporosis, fractures, and other chronic diseases no longer should be thought of as an inevitable part of growing old. By focusing on prevention and lifestyle changes, including physical activity and nutrition, as well as early diagnosis and appropriate treatment, Americans can avoid much of the damaging impact of bone disease and other chronic diseases.

— Tommy G. Thompson

Introduction

This quote is from an introduction to Bone Health and Osteoporosis: A Report of the Surgeon General, published in 2004 (Thompson was Secretary of Health and Human Services at the time). It was the first Surgeon General’s report ever published on bone health, and it pointed out the high risk of disabling fractures, particularly in postmenopausal women.

For all clinicians who treat peri- and postmenopausal women, the message from that report should be clear: prevention is preferable, early and systematic identification of high-risk patients is both possible and important, and appropriate treatment is crucial.

Research in prevention of fractures has made huge strides since alendronate was first approved in 1996. In the last 15 years, the number of safe and effective treatments has grown, and both professional and lay media have given clinicians and patients a good sense of the benefits that pharmacologic therapy offers, as well as a better sense that serious treatment-related risks are extremely rare.

Further, with efforts to systematically pool and use information from around the world about bone density and risk factors for fractures, we have been able to provide much better assessments of risks for individual patients to help guide decisions about the best possible treatment.

Finally, several treatments now are in development aimed to increase bone formation. In particular, the most novel ones hold the prospect of substantially reducing fracture risk to “normal” for an individual patient’s age—or even for that diagnostic benchmark, the “young normal” 30-year-old.

This supplement provides an overview of the state of the art of osteoporosis diagnosis and treatment, as well as a glimpse into new avenues of pharmacologic intervention.

— Steven R. Cummings, MD, FACP

Osteoporosis is a disorder characterized by reduced bone strength and, consequently, an increased risk for fractures over time. Menopause is an important risk factor for these changes in bone because estrogen levels decrease, triggering accelerated bone loss for the next 5 to 10 years. After this, slower bone loss will continue indefinitely. During the postmenopausal years, the bone mineral density (BMD) measurement—which is an estimate of bone quantity or mass—reflects how much bone was built during the bone-building years (which ends in one’s late 20s to early 30s) and how much bone has been lost since the onset of menopause.

Although it is likely that bone is lost between the time an individual achieves peak bone mass in her mid-20s to early 30s and the perimenopausal period, this is a very slow, gradual loss that is not clinically significant in most cases. In contrast, postmenopausal bone loss involves important changes not only in the quantity of bone but also in its microarchitecture and, therefore, its “quality” (Figure). These microarchitectural changes contribute to the weakening of bone and increase the susceptibility to fractures with relatively low trauma.

### Risk Factors for Osteoporosis and Fractures

In women, postmenopausal estrogen depletion is a major risk factor for osteoporosis and increased risk for fractures, but individual risk also varies according to how much bone mass was accumulated during the bone-building years, culminating in the peak bone mass achieved, and also is affected by a number of conditions, diseases, and medications that may cause or contribute to bone loss or reductions in bone formation that may lead to osteoporosis and fractures. These include genetic factors; hypogonadal states; certain endocrine, gastrointestinal, and hematologic disorders; rheumatic and autoimmune diseases; neurologic and musculoskeletal risk factors; and medications such as glucocorticoids, some antiepilepsy drugs, and certain cancer treatments. Among the most common risk factors for loss of bone mass and impairment of bone quality—and for increased fracture risk—are several that are modifiable because they are associated with lifestyle and behavior (Table 1).

Two of these risk factors bear further comment here. The first is body mass. It has long been recognized that thinner individuals are at increased risk for osteoporosis and fractures, and this has led to a common misperception that higher body mass—including obesity—confers some degree of protection against fractures. This latter point is not necessarily correct, and obesity currently is being studied more thoroughly with respect to its relationship to fractures. Obesity often is associated with type 2 diabetes, and that condition recently has been recognized as being associated with an increased risk for fractures. The second is falling as a risk factor for fractures. Prevention of falls must be considered in the management of all patients at risk for osteoporosis and, in particular, for older individuals with established osteoporosis.

### Evaluating Osteoporosis and Fracture Risk

No clinical tool is commonly available that allows an evaluation of the microarchitectural changes that have evolved, but assessment for risk factors for osteoporosis and fractures and measurement of BMD provide useful information to guide patient management decisions, including the choice of whether to institute pharmacologic therapy.

#### Table 1. Lifestyle and Behavioral Risk Factors for Osteoporosis and Fractures

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>≥3 drinks/day</td>
</tr>
<tr>
<td>Aluminum</td>
<td>(in antacids)</td>
</tr>
<tr>
<td>Excess vitamin A</td>
<td></td>
</tr>
<tr>
<td>Falling</td>
<td></td>
</tr>
<tr>
<td>High caffeine intake</td>
<td></td>
</tr>
<tr>
<td>High salt intake</td>
<td></td>
</tr>
<tr>
<td>Immobilization</td>
<td></td>
</tr>
<tr>
<td>Inadequate physical activity</td>
<td></td>
</tr>
<tr>
<td>Low calcium intake</td>
<td></td>
</tr>
<tr>
<td>Smoking (active or passive)</td>
<td></td>
</tr>
<tr>
<td>Thinness</td>
<td></td>
</tr>
<tr>
<td>Vitamin D insufficiency</td>
<td></td>
</tr>
</tbody>
</table>

Source: National Osteoporosis Foundation.
The Surgeon General’s report on bone health and osteoporosis indicates that one out of every two women and one out of four men more than 50 years of age experience an osteoporosis-associated fracture at some point in their remaining lifetime. Clearly, early identification and appropriate treatment of higher-risk individuals are important.

**Risk Factor Assessment**

The first step in risk assessment is a simple review of the list of known risk factors for osteoporosis and fracture. A complete list and discussion of these risk factors can be found in the Clinician’s Guide to Prevention and Treatment of Osteoporosis, developed and published by the National Osteoporosis Foundation, and available online (http://nof.org/professionals/pdfs/NOF_ClinicianGuide2009_v7.pdf).

The primary care practice is the ideal setting for an initial risk factor assessment, which is easily incorporated into the protocol for annual physicals or other routine visits. This should be done for all individuals—not men and women—at around age 50 years. The assessment also should be done in any patient more than age 45 years who has sustained a fracture—prior fracture being an extremely powerful predictor of the risk for future fractures—and even earlier in patients who have medical conditions or are taking medications (particularly oral corticosteroids) that predispose them to bone loss.

The FRAX® Fracture Risk Assessment Tool, developed by the World Health Organization (WHO), is an excellent aid that is particularly suited to primary care practice. FRAX is discussed in a separate section below.

**Bone Density Measurement**

Measurement of BMD provides an indication of the level of bone mass and helps determine which individuals are at an increased risk for fracture. Although several types of BMD technologies currently are available (including peripheral dual-energy X-ray absorptiometry [peripheral DXA], computed tomography–based absorptiometry, and quantitative ultrasound densitometry), the type of BMD test done predominantly in the United States is central DXA of the spine and hip. The T scores derived from DXA are the measurements used in the WHO diagnostic classifications of normal BMD, osteopenia, and osteoporosis, and the BMD measurements discussed in this article refer to the DXA T scores at the spine or hip.

The absolute measurement of BMD is provided as grams of mineral per square centimeter (g/cm²) in the skeletal area scanned and is expressed as a T score. The T score compares the patient’s BMD with the average value in young normal individuals. A “young normal” is defined as a healthy 30-year-old individual at peak bone mass. Z scores are also reported and reflect the patient’s BMD as compared to what is expected in age-matched peers.

The WHO diagnostic classifications (Table 2) are based on the difference between the patient’s measured BMD and the young normal mean. T scores above –1.0 indicate normal bone density. Low bone density (osteopenia) is indicated by T scores between –1.0 and –2.5; a T score of –2.5 or lower is diagnostic for osteoporosis. Each standard deviation of difference in the T score is equal to a 10% to 15% decrease in bone density (eg, an individual with a T score of –2.0 has a BMD 10%–15% lower than that in someone with a T score of –1.0).

The National Osteoporosis Foundation’s Clinician’s Guide to Prevention and Treatment of Osteoporosis recommends DXA for individuals 50 years of age or older who have risk factors for osteoporosis and fractures. Men with no osteoporosis/fracture risk factors should have their first DXA at age 70 years, and it is reasonable to delay DXA until age 65 years in women whose only risk factor is menopause. In these patients, it is important for risk factor assessment to be repeated regularly; if new risk factors are identified, then DXA should be done sooner.

It has been suggested that patients who have a good BMD score should have a follow-up DXA in 2 to 5 years. In the intervening time, repeat DXA is warranted if a fracture occurs or some other important risk factor emerges.

It also has been suggested that patients who are being treated for osteoporosis should have DXA between 1 and 2 years after starting therapy; if bone density has risen or is stable, DXA can be repeated every 2 years to confirm the stability of BMD. This is recommended because, in the real-world setting, a small proportion of treated patients will lose BMD despite therapy (eg, because of adherence issues or the development of medical comorbidities).

**Clinical Evaluation**

The presence of risk factors and a low score on DXA indicate the need for further clinical workup to identify or rule out secondary causes of low bone mass or osteoporosis. Depending on the condition or disease being considered, relevant blood and urine laboratory tests should be performed. Biochemical testing (including a complete blood count, serum calcium level, 25-hydroxy vitamin D level, creatinine level, and a liver panel) should be considered prior to beginning therapy in patients who have been diagnosed with osteoporosis.

Tests for markers of bone turnover—such as serum cross-linked C-terminal telopeptide (CTX) or urinary cross-linked N telopeptide (NTX)—provide an assessment of the rate of bone resorption, but this information is not diagnostic of osteoporosis, and the determination of normal ranges in postmenopausal women has not been fully established. For these reasons and because the cost of the tests can be high and may not be reimbursed by third-party payers, the main utility of testing for biochemical markers is in clinical trials of antiresorptive agents. Nevertheless, clinicians may find these tests useful in selected cases—for example, if a patient’s BMD appears to be going down without any clear reason and the correctness of the DXA test is questioned—to investigate whether the patient has additional evidence for bone loss.

<table>
<thead>
<tr>
<th>Table 2. Diagnosis of Osteopenia and Osteoporosis Based on DXA BMD Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T Score</strong></td>
</tr>
<tr>
<td>+1.0 to –1.0</td>
</tr>
<tr>
<td>–1.0 to –2.5</td>
</tr>
<tr>
<td>–2.5 or lower*</td>
</tr>
</tbody>
</table>

*BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry. *In this group, a history of one or more fractures indicates severe or "established" osteoporosis. Source: World Health Organization Technical Report."
Underdiagnosed and Underserved Populations

Several populations of people are at increased risk for fractures but are not evaluated:

- **Individuals with a fracture history** constitute the largest underdiagnosed and underserved population. In the orthopedic fracture setting, an overwhelming majority of older patients with a fracture that requires casting or internal fixation is not being directed for a medical assessment for secondary fracture prevention.

- **Men more than 70 years of age** typically are not screened, in large part because Medicare does not routinely reimburse for DXA testing for individuals in this population. The US Preventive Services Task Force currently is reassessing the role of screening in older men.

- **Screening of older African American women** generally is not adequate. In part, this may be the result of diminished access to any kind of medical care among the poor in this group, but, in many cases, this is the result of the misperception of risk in nonwhite populations. It must be understood that a lower risk is not the same as absence of risk.

- **Similarly, some Hispanics** may have a slightly lower risk for osteoporosis than “Caucasian” women, but it is important to remember that, although “Hispanic” is an important cultural and social designation, it is not necessarily a helpful descriptor from a medical standpoint. Ethnicity, country of origin, racial characteristics, and, therefore, levels of risk differ among women designated as Hispanic.

- **Asian Americans** (for purposes of this discussion, individuals of East Asian descent—Chinese, Japanese, and Korean) have a relatively low risk for hip fractures compared with Caucasians. For this reason, along with the fact that they are nonwhite, osteoporosis screening in Asian Americans frequently is overlooked. However, individuals in this population often are at increased risk for vertebral fractures as they age.

- **Women with surgically induced menopause** who are not treated with estrogen have more rapid bone loss, starting at an earlier age.

---

**FRAX**

The FRAX algorithm\(^4\) allows clinicians to perform a risk assessment using a specific set of common factors that have been well validated in long-term epidemiologic studies as contributing to an increased risk for fractures. The FRAX questionnaire is easy to use because most of the information is determined by patients’ answers to yes-no questions. The risk factors that are included in FRAX are listed in Table 3. The Fracture Risk Assessment Tool is available online at http://www.shef.ac.uk/FRAX.

The risk factors included in FRAX are present in populations worldwide, but their application has been individualized to specific countries based on the known fracture rates as well as mortality rates within each country. In the United States, FRAX can be used to assess both men and women and according to patients’ ethnicity or race. The result of the assessment is a 10-year absolute risk for hip fracture and also for the category of major osteoporotic fractures, a combination of shoulder, wrist, hip, and clinical spine fractures (ie, vertebral fractures that are symptomatic and lead to X-ray confirmation).

The risk factors assessed in FRAX were chosen because of their relative independence from BMD. When added to BMD, they improve risk assessment determination. However, 10-year absolute fracture risk can be obtained without BMD testing, an important consideration in parts of the world where the test is not available. Since BMD testing is widely available in the United States and is generally reimbursed by third-party payers, it is beneficial to have that result to enhance the value of an individual’s risk assessment.

The main value of FRAX is to help determine whether treatment is appropriate to prevent osteoporosis-related fractures; it is not validated to determine risk in patients who are already receiving treatment. The National Osteoporosis Foundation’s Clinician’s Guide recommends that those postmenopausal women and older men with T scores of −2.5 or below at the spine or hip and those with a prior hip or vertebral fracture be treated with pharmacologic therapy.\(^1\)

FRAX is most helpful, therefore, in patients with a BMD T score between −1.0 and −2.5, and the National Osteoporosis Foundation’s Clinician’s Guide recommends levels of 10-year absolute fracture risk based on FRAX at which treatment is cost-effective and should be considered—that is, greater than or equal to 3% for hip fracture or greater than or equal to 20% for major osteoporotic fractures.

**Indications for Considering Consultation or Referral**

An endocrinology specialist can provide helpful insights about treatment decisions for patients in whom a blood chemistry panel suggests the presence of severe vitamin D deficiency, primary hyperparathyroidism, or hypercortisolism.

Referral to or consultation with a specialist in osteoporosis should be considered when determining the treatment of choice in patients with severe osteoporosis (eg, when the T score is −3.5 or lower or the patient has already had multiple fractures). A consultation also is advisable in cases in which a patient experiences a fracture despite appropriate therapy or when the cause of continued BMD decreases has not been readily identified. Although the available pharmacologic modalities substantially lower the risk for fractures, no drug prevents all fractures in all patients. Finally, referral to a rheumatologist for pain management may be appropriate for a patient with multiple compression fractures.

**Conclusion**

A familiarity with osteoporosis and fracture risk factors, DXA testing and results, and patient evaluation using risk factor assessment and including the FRAX algorithm are key to appropriate management of continued on page 11
The goal of treatment in patients with osteoporosis is the prevention of fractures. Although it is not possible to eliminate the risk for fractures, currently available medications can substantially reduce that risk.

Fracture risk reduction begins with efforts to optimize skeletal health early in life. This includes optimizing the full genetic potential for achieving peak bone mass during the bone-building years (adolescence and young adulthood) and minimizing the bone loss that occurs thereafter. The foundation of any program for the management of osteoporosis is a healthy lifestyle (eg, regular physical activity and avoidance of smoking, excess alcohol intake, and medications known to be harmful to bone) and good nutrition (with particular emphasis on adequate calcium and vitamin D intake).

Clinical tools, such as bone density testing and the World Health Organization fracture risk assessment algorithm (FRAX®), can be used to identify patients who are at high risk for fracture and most likely to benefit from pharmacologic therapy. Methods for assessing risk are addressed in Dr Siris’s article beginning on page 4.

**Risk Reduction and Treatment: Evidence for Impact on Fractures**

A robust database has accumulated demonstrating the benefit of pharmacologic therapy in the management of osteoporosis. All of the drugs approved by the US Food and Drug Administration (FDA) for the prevention and treatment of postmenopausal osteoporosis have demonstrated clinical benefit in randomized, placebo-controlled clinical trials. Each of these drugs has been shown to reduce the risk for vertebral fractures, and some also have been shown to reduce the risk of hip and other nonvertebral fractures.

Estrogen is approved for the prevention but not for the treatment of postmenopausal osteoporosis. Although data from the National Institutes of Health’s Women’s Health Initiative show that estrogen replacement therapy can reduce the risk of fractures as well as prevent the development of osteoporosis, the FDA has not approved estrogen for treatment of osteoporosis.

**Options for Osteoporosis Therapy**

Drugs for the treatment of osteoporosis are classified as antiresorptive (also called anticonletic) and osteoanabolic (bone forming). Recent advances in our understanding of the molecular regulators and mediators of bone remodeling have identified new potential targets for therapeutic intervention, resulting in the development of novel compounds aimed at treating osteoporosis and other skeletal diseases (Table).

**Antiresorptive Agents**

The onset of menopause usually is accompanied by an increase in the rate of bone remodeling (turnover) with an imbalance of bone resorption exceeding bone formation. If this imbalance continues long enough, bone mass is lost, osteoporosis may result, skeletal fragility develops, and the risk of fracture increases. All of the antiresorptive agents work by restoring the bone remodeling rate to a lower level and improving the balance of resorption and formation. With slower turnover, the bone has fewer resorption pits and becomes better mineralized. This results in stronger bone and, consequently, a reduction in fracture risk.

The class of antiresorptive agents known as bisphosphonates comprises the drugs used most commonly to manage osteoporosis. Three oral agents in this class (alendronate, risedronate, and ibandronate) and two intravenous formulations (ibandronate and zoledronate) currently are available. Alendronate, available in generic form and therefore usually available at comparatively low cost, is given weekly. The two other oral bisphosphonates (risedronate and ibandronate) offer the convenience of monthly dosing.
Other antiresorptive agents include raloxifene (a selective estrogen receptor modulator, or SERM, also referred to as an estrogen agonist/antagonist), nasal calcitonin and denosumab. Raloxifene has a particular advantage in that it reduces the risk for invasive breast cancer, so this may be an appropriate choice for patients at increased risk for breast cancer. Calcitonin, given daily by the intranasal route, is approved for use in women who are at least 5 years postmenopausal. It is perhaps the least robust of all the agents under discussion in terms of reducing fracture risk, but it may be the most appropriate for use in patients in whom drug-drug interactions are a concern, as no such interactions have been identified with calcitonin. In addition, the convenience of nasal administration may make this agent useful in patients who may have a difficult time managing the scheduling and fasting requirements associated with the oral bisphosphonates.

**Osteoanabolic Agent**

For patients who are at very high risk for fracture, the osteoanabolic agent teriparatide should be considered. Teriparatide works by increasing bone turnover, with bone formation greater than resorption. There is good evidence that treatment with teriparatide results in bone being formed at sites where it has been lost. There is an increase in trabecular thickness and a decrease in the spacing between trabeculae; there may also be a thickening of cortical bone and a modest enlargement of bone. Greater bone size is associated with improvement in bone strength.

Based on clinical trial data, the FDA-approved duration of treatment with teriparatide is a maximum of 2 years. After this time, patients previously treated with this agent must switch to therapy with an antiresorptive agent to maintain the benefit that has been achieved.

**Novel Agents**

The options for osteoporosis therapy have broadened recently with the development of novel agents that target regulatory pathways of bone remodeling. In his article beginning on page 10, Dr Cummings addresses the agents that are still in clinical trials or in earlier phases of development. The first of these newer drugs, denosumab, was approved recently for the treatment of osteoporosis in postmenopausal women at high risk for fracture and is discussed here.

Denosumab is a fully human monoclonal antibody that binds to the receptor activator of nuclear factor-κB ligand (RANKL, or RANK ligand)—a cytokine that is the principal mediator and regulator of osteoclastic bone resorption. In a sense, RANK ligand can be thought of as the final common pathway for the regulation of osteoclastic bone resorption, and by directly affecting this cytokine, denosumab exerts a potent antiresorptive effect. In phase III clinical trials, denosumab was shown to reduce the risk of vertebral fractures, nonvertebral fractures, and hip fractures in postmenopausal women with osteoporosis.15,16

It has several potential advantages over some of the currently available medications in that it is dosed infrequently—once every 6 months—with infrequent dosing often being associated with improved long-term compliance and persistence. It is given by subcutaneous injection, circumventing any concerns about gastrointestinal (GI) absorption. In addition, because denosumab is administered subcutaneously, it can be given in settings such as a primary care practice that typically would not have the staff or facilities to administer intravenous infusions.

**Safety of Osteoporosis Treatments**

The safety profiles of all of these agents are generally good. Important information about adverse events, precautions, and warnings are summarized below.

**Bisphosphonates**

The experience from randomized, controlled trials shows that GI side effects in patients taking oral bisphosphonates are no different than in patients taking placebo. However, postmarketing studies have shown that about 20% of patients discontinue taking oral bisphosphonates after a period of time because of concerns about GI intolerance.17,18 For those patients, some other therapeutic agent must be considered. Within the bisphosphonate class, ibandronate and zoledronate are available in intravenous formulations, administered every 3 months and every 12 months, respectively.

**Raloxifene**

In clinical trials, women treated with the SERM raloxifene had an increased risk for venous thromboembolism (VTE)19; postmenopausal women with documented coronary heart disease or who were at increased risk for coronary events were at an increased risk for death due to stroke (although not for nonfatal stroke).20,21 The drug is contraindicated in women with VTE or a past history of VTE (including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis), and risk versus benefit should be considered carefully in women at risk for stroke (risks including prior stroke, transient ischemic attacks, atrial fibrillation, hypertension, or cigarette smoking).

**Intranasal Calcitonin**

Widespread clinical experience with this agent since it was introduced in 1995 has shown that intranasal calcitonin is generally safe, being associated with only minimal side effects.22 In the largest study to date of intranasal calcitonin, the PROOF (Prevent Recurrence of Osteoporotic Fractures) study, Chesnut and colleagues23 found a significant increase in rhinitis and, interestingly, a significant decrease in headache in patients treated with calcitonin.

**Teriparatide**

Clinical studies have demonstrated an increased incidence of nausea, dizziness, and leg cramps with teriparatide.24,25 In addition, preclinical studies showed that administration of teriparatide was associated with the development of osteosarcoma in rats, and although the relevance of this finding in humans has not been determined, the prescribing information for teriparatide states that it should not be used by patients who are at risk for osteosarcoma (eg, those with Paget’s disease of bone, unexplained elevations of alkaline phosphatase, children and young adults with open epiphyses, or individuals with a history of radiation therapy involving skeleton).

**Denosumab**

Based on the clinical trials of denosumab, the prescribing information26 notes that serum calcium levels may decrease with denosumab therapy, particularly in patients with renal impairment, and patients with hypocalcemia should not receive denosumab until this condition is corrected. In addition, adequate supplementation with calcium and vitamin D should be given during therapy with this drug.

Serious skin infections may also occur, so patients should be advised to consult a physician if signs or symptoms of skin infection occur. Dermatitis, rashes, and eczema also have been reported, and denosumab
should be discontinued if symptoms are severe. Also, patients using this medication should be monitored for symptoms of osteonecrosis of the jaw and oversuppression of bone turnover. Pancreatitis also has been reported in clinical trials.

**Improving Treatment Compliance and Persistence: Shared Decision Making**

Despite the best efforts of health care professionals over many decades, our society remains predominantly sedentary, and nutritional choices too often tend to be poor (deficient calcium intake and low serum levels of 25-hydroxy vitamin D are quite common). Nevertheless, to increase our effectiveness in reducing osteoporosis-related fractures, clinicians must continue to emphasize the importance of a healthy lifestyle that includes regular physical activity (particularly weight-bearing exercise to benefit the skeleton) and good nutrition (with a particular focus on adequate calcium and vitamin D intake).

Patients who have been identified as being at increased risk for osteoporotic fractures can benefit from pharmacologic therapy, but only if the drugs are taken appropriately and for a long enough period of time to confer benefit. One process for improving pharmacologic therapy compliance, adherence, and persistence is shared decision making, where the clinician and patient work collaboratively and both have all of the appropriate information available to them.

The clinician must ensure that the patient has a good understanding of the nature of the disease that is being discussed. With regard to osteoporosis, the patient should be told and fully understand the potential clinical consequences of osteoporosis (in terms of fracture risk) and the potential result of fractures (in terms of disability, loss of independence, and, in the case of vertebral and hip fractures, increased mortality). Although the risks of pharmacologic treatment for osteoporosis generally are quite small, some of these actual and theoretical adverse events have been given a great deal of attention in the lay media, so some patients may have an exaggerated view of the side effect risks.

At the same time, patients must share with their clinician their own personal biases about therapy, goals for treatment, previous experiences with osteoporosis therapy, and their preferences once the options have been fully explained to them.

When the clinician fully understands the patient’s point of view and when the patient fully understands what the clinician is saying, they can negotiate a treatment plan that makes sense and is acceptable to both.

Once treatment is started, a plan for appropriate follow-up should be set. With a long-term course of treatment—as is required with pharmacologic agents used in osteoporosis therapy—it is not useful to prescribe a medication and simply ask the patient to return in a year or two for follow-up. Patients may become confused about how to take the drug during this time, may lose their motivation to continue taking it, or may not be taking it correctly.

Instead, consider scheduling a return office visit or contact by a health care professional within a few months of starting treatment to ensure that the patient filled the prescription, is taking the medication correctly, is not having any problems or side effects, and is continuing to take calcium and vitamin D at the same time. In addition, periodic monitoring of the benefit of therapy provides feedback for patients that may provide additional motivation to continue using the medication and allows the clinician to identify patients who are not responding as well as expected and who need further evaluation and, perhaps, a change in the treatment plan.

**Conclusion**

The incidence of osteoporosis and related fractures is high, but many effective and safe pharmacologic strategies are now available to manage this condition and reduce the risk for fractures. The clinical challenge is threefold: to identify patients most likely to benefit from therapy, to start those patients on appropriate treatment, and to follow those patients to ensure that the medications prescribed are being taken correctly and for a long enough period of time so that the maximum benefit can be derived.

**To increase our effectiveness in reducing osteoporosis-related fractures, clinicians must continue to emphasize the importance of a healthy lifestyle.**

**References**


continued on page 11
Recently, a novel agent for the treatment of osteoporosis was approved by the US Food and Drug Administration (FDA). This agent, denosumab, is an antibody to the receptor activator for nuclear factor κ-B ligand (RANKL, or RANK ligand), a protein that is crucial to osteoclastogenesis—the formation, function, and survival of osteoclasts. Briefly, denosumab binds to RANKL, blocking its action and inhibiting osteoclast development and activity.

The clinical trial of the prevention of fractures in postmenopausal women with osteoporosis—called the FREEDOM trial (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease)—demonstrated that denosumab decreased bone resorption by more than 90%, decreased the risk for vertebral fracture by about 70%, decreased the risk for hip fractures by 40%, and decreased the risk for all nonvertebral fractures by 20%.

Ongoing research to discover and develop a larger range of options for the treatment of osteoporosis and, therefore, the prevention of related fractures has revealed other novel pathways for either inhibiting bone resorption or increasing bone formation. A number of potential new treatments currently are in phase II or III clinical trials. This article provides a brief overview of some of the most promising investigational agents.

New Selective Estrogen Receptor Modulators

Several new selective estrogen receptor modulators (SERMs) resemble the first agent in this class, raloxifene. SERMs can have either estrogen receptor agonist activity or antagonist activity, depending on the target tissue—for example, in bone, SERMs produce estrogen-agonist effects but have estrogen-antagonist activity in breast tissue. Clinical trials have demonstrated that treatment with certain SERMs maintains bone mineral density (BMD), including the BMD of vertebrae and hip bone, and reduces the risk for vertebral fractures.

The newer agents seem to have more potent estrogenic effects on bone than are seen with raloxifene and, at the same time, may not be associated with increased endometrial thickness or other uterine effects, a concern that developed with other SERMs that were being investigated for postmenopausal osteoporosis.

One of these agents, bazedoxifene, was studied in a phase III clinical trial of patients with postmenopausal osteoporosis, in which bazedoxifene was compared to raloxifene and placebo. The use of bazedoxifene significantly reduced the incidence of new vertebral fractures compared to placebo, and reduced the incidence to the same degree that raloxifene did. In addition, BMD significantly increased in subjects taking bazedoxifene compared to placebo recipients; these were comparable to BMD increases seen with raloxifene.

Combinations of several doses of bazedoxifene combined with several doses of conjugated estrogen (Premarin®) also have been studied. In a phase II placebo-controlled trial, most of the combinations increased BMD. Further study is required to establish whether the combination reduces fracture risk, and to determine its effects on breast cancer risk and cardiovascular events.

Two other SERMs have been developed—lasofoxifene and arzoxifene. Lasofoxifene has been shown to decrease both vertebral and nonvertebral fractures. It also is associated with a decreased incidence of breast cancer, cardiovascular events, and stroke, although deep vein thrombosis and pulmonary embolism are possible adverse events. Lasofoxifene is approved for use in Europe.

Arzoxifene, a very potent SERM, was initially developed for the prevention and treatment of breast cancer and also was investigated for the prevention and treatment of postmenopausal osteoporosis. Early animal and clinical studies suggested that arzoxifene reduces bone turnover, prevents bone loss, and maintains bone strength. However, a recently published clinical trial showed that arzoxifene compared to placebo significantly reduced vertebral fracture risk, but the reduction was no greater than the vertebral fracture risk reduction that has been demonstrated with raloxifene compared to placebo. In addition, arzoxifene failed to significantly reduce nonvertebral fracture risk. The study also demonstrated a trend toward a greater risk for endometrial cancer, so it will not be considered by the FDA for approval in the United States.

Cathepsin K Inhibitors

Cathepsin K (CatK) is a protease—that is, an enzyme produced by osteoclasts that degrades the protein matrix of bone. The greatest potential value of CatK inhibitors, as a class, is that they may decrease bone resorption without decreasing bone formation, and their antiresorptive activity is quickly reversible.

One of these agents, odanacatib, is an antiresorptive agent that improves bone density by blocking the resorption of proteins. This limits bone resorption to shallow pits, theoretically decreasing resorption while allowing full bone formation. It is possible that odanacatib actually promotes bone formation, although no increase in markers of bone formation have been identified.
Experiments with CatK-knockout mice showed that the animals treated with odanacatib had greater bone mass than control mice did, and the results of a phase II clinical study showed that treatment with odanacatib significantly increased bone density in the spine and hip compared to placebo. Whether it reduces the risk for fractures—particularly, nonvertebral fractures—to a greater degree than do the currently available osteoporosis treatments is being investigated in phase III trials, now under way.

Antisclerostin Antibody

Sclerostin is a molecule produced by mature osteocytes; it is not found in any other cell. Sclerostin is produced in response to decreased loading. It works by inhibiting the formation of osteoblasts, reducing the amount of new bone formation and, therefore, adversely affecting bone strength and increasing the risk for fracture.

Experimental studies show that antisclerostin antibodies increased both the mass and the strength of bone in rodents and primate models. In fact, antisclerostin antibodies appear to be the most potent bone-forming agents yet developed, with the potential to rapidly restore bone mass and architecture to normal. A recent publication described the results of a phase I study of an antisclerostin antibody in healthy volunteers. Compared with placebo, 3 months of treatment with the antisclerostin antibody increased bone density by up to 5% in the spine and 3% in the total hip. These reductions are larger than those seen with antiresorptive treatments 1 year, and appear to be greater than the effect seen with teriparatide. Phase II clinical studies of anti-sclerostin antibody are under way to determine the optimum dose and duration of therapy.

Conclusion

New treatments based on fundamental mechanisms currently are in various stages of development. The first of these agents targeting new pathways of therapy, denosumab, is the most potent antiresorptive agent developed to date. The agents discussed in this article demonstrate that targeting recently identified fundamental mechanisms of bone turnover hold promise for novel, effective pharmacologic treatments.

References


Identifying and Reaching Patients With Postmenopausal Osteoporosis: Where Should We Look? How Should We Test?

patients with or at increased risk for osteoporosis. The primary care clinician is in an excellent position to identify individuals at increased risk for osteoporosis and to use the available assessment tools to determine whether pharmacologic treatment is appropriate. Consultation with or referral to other clinical specialists can be considered in selected cases.

References


Osteoporosis Treatment: Defining Goals, Optimizing Strategies


EVALUATION FORM

We would appreciate your answering the following questions in order to help us plan for other activities of this type. Please print.

Name: ________________________________  
Specialty: ________________________________  
Degree:  
MD  D0  PharmD  RPh  NP  RN  BS  PA  Other  
Address: _______________________________________________________________  
City: ___________________ State: ___________ ZIP: ___________  
Telephone: __________________ Fax: ____________________  
E-mail: ________________________________  
Signature: ________________________________  
(All information is confidential.)

CME CREDIT VERIFICATION: I verify that I have spent _______ hour(s)/_______ minutes of actual time working on this CME activity. No more than 1.5 CME credit(s) will be issued for this activity.

PRETEST ASSESSMENT: Please rate your current knowledge of osteoporosis on a scale of 1 to 5, with 1 being the lowest and 5 the highest.  
1  2  3  4  5

POST-TEST ASSESSMENT: Please rate your current knowledge of osteoporosis on a scale of 1 to 5, with 1 being the lowest and 5 the highest.  
1  2  3  4  5

COURSE EVALUATION: Please evaluate the effectiveness of this activity by circling your choice on a scale of 1 to 5, with 1 being the lowest and 5 the highest.  
1  2  3  4  5

1. Describe the etiology of postmenopausal osteoporosis and explain the importance of disease and fracture prevention.  
2. Relate the reasons why postmenopausal osteoporosis is not adequately recognized and treated, particularly in certain populations.  

3. Discuss measures that could be taken to improve adherence to treatment.  
4. Explain how the World Health Organization’s FRAX algorithm and dual-energy X-ray absorptiometry can be used in primary care practice to identify patients who are at risk for osteoporosis and who may be candidates for pharmacologic intervention for prevention and/or treatment.  
5. Identify pharmacologic agents that are currently available to prevent and treat postmenopausal osteoporosis and describe their benefits and limitations.  
6. List and describe the newer agents for the treatment of osteoporosis that currently are in clinical trials.  
7. How do you rate the overall quality of the activity?  
8. How do you rate the educational content of the activity?  
9. After participation in this activity, have you decided to change your practice or treatment?  
10. Was the presented information fair, objective, balanced, and free of bias in the discussion of any commercial product or service?  
11. Suggested topics for future activities:

Copyright © 2010 Elsevier Inc.