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Review Article

Current and Emerging Pharmacologic Therapies for the Management of Postmenopausal Osteoporosis

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Abstract

Postmenopausal osteoporosis is an asymptomatic skeletal disease that is often underdiagnosed and undertreated. Osteoporotic fractures are associated with substantial morbidity and mortality and impaired quality of life—socially, emotionally, and financially. Considering the growing burden of osteoporotic fractures worldwide, there remains an ongoing need for progress in the diagnosis of osteoporosis, identification of individuals at high fracture risk, and treatment to prevent fractures. Adequate intake of calcium and vitamin D is recommended as baseline therapy for osteoporosis prevention and treatment. Available pharmacological agents for the management of postmenopausal osteoporosis may not be appropriate for all women. Oral bisphosphonates are generally considered first-line therapy for patients with osteoporosis, but their use may be limited by gastrointestinal side effects. Other agents include hormone therapy, the selective estrogen receptor modulator (SERM) raloxifene, salmon calcitonin, teriparatide (human recombinant parathyroid hormone), and strontium ranelate (in some countries). Factors that may contribute to poor compliance and persistence with current osteoporosis therapies include drug intolerance, complexity of dosing regimens, and poor understanding of the relative benefit and risk with treatment. Emerging therapies for postmenopausal osteoporosis include novel SERMs (bazedoxifene, lasofoxifene, ospemifene, arzoxifene) and denosumab. Because SERMs can display mixed functional estrogen receptor agonist or antagonist activity depending on the target tissue, they may confer beneficial effects on bone with limited stimulation of other tissues (e.g., breast, endometrium). Clinical investigation of these promising new agents is ongoing to evaluate efficacy and safety, with the goal of developing effective strategies to maximize long-term tolerance, compliance, and persistence with therapy.

Introduction

Postmenopausal osteoporosis is a silent (asymptomatic) disease characterized by decreased bone density and changes in bone microarchitecture that reduce bone strength and increase the risk of fractures.[1] Although there are a number of approved agents for the prevention or treatment (or both) of postmenopausal osteoporosis, available options may not be appropriate for all women, primarily because of safety and tolerability concerns. Combined with the significant impact of osteoporotic fractures on a global scale, there remains an ongoing need for new therapies that are efficacious while minimizing adverse clinical outcomes. Because it is asymptomatic, osteoporosis is often underdiagnosed and undertreated, so that most patients who suffer fractures have not received previous antiresorptive therapy.[2,3] Furthermore, treatment for osteoporosis is often associated with low long-term patient compliance and persistence, which can limit the effectiveness of therapy.[4,5] The purpose of this article is to describe the prevalence and burden of postmenopausal osteoporosis, to examine challenges with current therapies, and to evaluate emerging treatment options.

Epidemiology

The prevalence of osteopenia and osteoporosis increases with age, with the majority of cases occurring in postmenopausal women.[1] Approximately 200 million individuals around the world are affected, including one third of women between the ages of 60 and 70 years and two thirds of women $\geq$80 years.[6] Epidemiological data from the Third National Health and Nutrition Examination Survey (NHANES III)[7] showed that the incidence of osteopenia (bone mineral density [BMD] T-score between -1.0 and -2.5) was 37%–50% in American women $\geq$50 years, whereas the incidence of osteoporosis (T-score -2.5 or less) was 13%–18%.

A prospective analysis of data from 1142 patients $\geq$40 years with T-scores -2.0 or less in the Canadian Database

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for Osteoporosis and Osteopenia[8] showed that the risk of a first fracture increased by 3% for each advancing year of age (or by 18% for every 5 years). It has been estimated that the remaining lifetime risk of sustaining an osteoporotic fracture for an American woman 50 years of age is 40%, with the majority of fractures occurring after 75 years of age.[9]

The association between BMD and fracture risk is well established. The proportion of hip and spine fractures that are attributable to low bone density at these skeletal sites has been estimated to be 80% in women between 45 and 64 years of age and 90% and 95% in those aged 65–84 years and ≥85 years, respectively.[10] Although the risk of fracture increases as BMD declines, there are numerically more fractures in those individuals with osteopenia than those with osteoporosis because so many more patients are in this category. The Study of Osteoporotic Fractures,[11] which followed a cohort of postmenopausal women ≥65 years for 5 years, showed that 54% of hip fractures occurred in women who did not have osteoporosis according to the World Health Organization (WHO) criteria.

Despite the availability of diagnostic tools and evidence supporting the efficacy of preventive measures and treatments for osteopenia and osteoporosis, a significant proportion of those afflicted remains undiagnosed and untreated.[12] The multinational IMPACT study[13] assessed the accuracy of radiographic diagnoses of vertebral fracture in women aged 65–80 years who were newly diagnosed with osteoporosis based on BMD measurements. Of 2451 women with evaluable lateral spine radiographs, 789 (32%) were found to have at least one vertebral fracture, and 266 (34%) of these women were not recognized as having a vertebral fracture in reports by local radiologists.

In a Danish study[3] that analyzed hospital records for patients diagnosed with osteoporosis or osteoporotic fractures, the annual incidence of osteoporosis in women ≥50 years old was estimated to be 58,568 per million inhabitants; however, only 4,823 cases were diagnosed, representing just 8.2% of the expected figure. In addition, only 28% of women who experienced a fracture had received previous antiresorptive drug therapy. Similar results were obtained in a Japanese study,[2] in which 367 of 422 (87%) patients with osteoporosis-related fractures did not report any drug treatment before or after the incident fracture. Findings from an American study[14] of 95 patients ≥65 years undergoing surgery for hip fracture indicated that none of them received a bone density scan during hospitalization or were scheduled to have it as an outpatient procedure, and only 2% reported receiving pharmacological therapy for osteoporosis at discharge.

Impact of Osteoporotic Fractures on Health Outcomes

The consequences of osteoporotic fractures include increased morbidity and mortality, as well as adverse effects on quality of life—socially, emotionally, and financially.[15,16] Hip fractures are regarded as the most devastating type of osteoporosis-related fractures; this may be due, in part, to loss of mobility and the resulting need for long-term care in many cases, as the average age at which hip fracture occurs is 82 years.[1] However, other types of fractures can also have a substantial impact on health-related quality of life. For instance, multiple or severe vertebral fractures may be associated with significant pain, reduced pulmonary function, loss of height, and kyphosis, which can restrict movement and increase the risk of further falls and fractures.[1,17–19] In addition, sustaining vertebral fractures has been shown to significantly impact emotional status.[20]

In a study[21] that evaluated the quality of life in postmenopausal women with osteoporosis using validated questionnaires (Qualeffo-41, Zung), 55% of osteoporotic women with fractures had a reduced quality of life compared with 32% of osteoporotic women without fractures and 11% of controls. For women with vertebral fractures, Qualeffo scores for pain, physical function, social function, and health perception parameters were significantly worse than in controls ($p < 0.001$). Moreover, a greater percentage of osteoporotic women with or without fractures (40%) experienced symptoms of depression compared with control patients (23%).[21] A recent cross-sectional study[22] showed that postmenopausal osteoporotic women with prevalent vertebral fractures had a significantly greater incidence of depressive symptoms than those without prevalent vertebral fractures as assessed by the Geriatric Depression Scale ($p < 0.001$).

Fractures are associated with significant mortality. Results of the Fracture Intervention Trial[23] in postmenopausal women with low bone mass indicated that the risk of mortality after suffering a hip fracture was nearly 6 times greater and nearly 9 times greater following a spine fracture than those who did not experience a clinical fracture. Findings from another study[24] demonstrated an excess mortality of approximately 20% over a 5-year period in women with hip and vertebral fractures.

Taken together, substantial evidence underscores the need for improved efforts in the management of postmenopausal osteoporosis. This includes a greater recognition of the disease, particularly in the identification of individuals at high risk for fracture. An algorithm for determination of fracture risk recently developed by the WHO, the Fracture Risk Assessment Tool (FRAX®), is an important advance in this regard.[25,26] It takes into account validated clinical risk factors for fracture in addition to BMD and may serve as a useful tool in facilitating treatment decisions.

Challenges with Current Strategies for Management of Osteoporosis

Prevention is an important part of dealing with any disease, and the National Osteoporosis Foundation (NOF) guidelines[27] recommend BMD testing in all women aged ≥65 years and men aged ≥70 years. Younger postmenopausal women and men aged 50–69 years should be tested if their clinical risk factor profile reveals cause for concern. BMD assessment is also recommended for women in the menopausal transition with a specific risk factor (e.g., low body weight, prior low trauma fracture, or high-risk medication), adults >50 years of age who experience a fracture, adults with a condition or taking a medication associated with low bone mass or bone loss, and anyone taking or considering treatment for osteoporosis or showing evidence of bone loss. In addition, postmenopausal women discontinuing estrogen-based therapy should be tested. The guidelines recommend repeat BMD testing every 2 years for patients being treated for osteoporosis. More frequent testing may be warranted in certain clinical situations.[27]

Nonpharmacological strategies to reduce the risk of fracture include lifestyle modification (e.g., smoking cessation

and limiting alcohol and caffeine use), nutritional guidance/dietary supplementation, and physical exercise.[28] The NOF[27] recommends pharmacological intervention for postmenopausal women and men aged ≥50 years with hip or vertebral (clinical or morphometric) fracture, a BMD T-score of ≤−2.5 at the femoral neck or spine, or a BMD T-score between −1.0 and −2.5 at the femoral neck or spine and a 10-year probability of a hip fracture ≥3% or a major osteoporosis-related fracture ≥20% based on the FRAX®. Available therapies include bisphosphonates, hormone therapy, raloxifene, salmon calcitonin, and parathyroid hormone (Table 1). Most of these are antiresorptive agents that improve bone strength and reduce the risk of fracture primarily by decreasing bone turnover and maintaining or increasing BMD. Anabolic agents (i.e., parathyroid hormone) exert their effects by increasing bone formation.

Vitamin D and calcium supplementation

Adequate intake of vitamin D/calcium is recommended as an inexpensive baseline therapy for the prevention and treatment of osteoporosis for all patients and is included in most clinical trials evaluating newer therapeutic osteoporosis agents.[29,30] Evidence suggests that vitamin D/calcium supplementation may have favorable effects on BMD and even reduce the risk of fracture,[31–34] although some recent randomized controlled clinical trials have shown no evidence of a reduced fracture risk with vitamin D/calcium supplementation.[34–36] Calcium supplementation has shown little effect in the first 5 years of the menopausal transition, when the majority of bone loss can be attributed to decreased estrogen production.[31] A meta-analysis[37] showed that the treatment effect is greatest with calcium doses of ≥1200 mg.

Vitamin D deficiency is common in adults and can be caused by lack of sun exposure, intestinal fat malabsorption problems, and sequestration of vitamin D in the body fat in obese individuals.[29] Measurement of 25(OH)D (the major circulating form of vitamin D) is recommended for patients with low BMD, as vitamin D deficiency contributes to osteopenia and osteoporosis.[29] Exposure to sunlight, often combined with adequate supplementation, has been suggested to be the first-line treatment for patients with vitamin D deficiency.[29] Of the two forms of vitamin D, ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3), cholecalciferol appears to be more potent in increasing the level of circulating vitamin D and is the preferred form of supplementation.[28] The greatest treatment effect is observed with doses of vitamin D of ≥800 IU.

Additional benefits of vitamin D/calcium supplementation in elderly people are a notable reduction in the incidence of falls, which may be attributed to effects on muscle strength and balance,[38–40] and a possible reduction in cancer risk.[41]

Table 1. FDA[a]-Approved Therapies for Postmenopausal Osteoporosis

	Prevention	*Treatment*
Bisphosphonates		
Alendronate	x	x
Risedronate	x	x
Ibandronate[b]	x	x
Zoledronic acid		x
Raloxifene	x	x
Systemic estrogen products	x	
Teriparatide		x
Salmon calcitonin		x

[a]FDA, Food and Drug Administration.
[b]Intravenous injection (4 times per year) approved for treatment only. Oral formulation approved for prevention and treatment.

Bisphosphonates

Bisphosphonates are generally considered first-line therapy for patients with osteoporosis. Numerous studies[42–49] have shown that bisphosphonates lead to significant improvements in BMD and reductions in vertebral and nonvertebral fracture risk (approximately 20%–50% relative to placebo) in postmenopausal women with osteoporosis. However, evidence suggests that oral bisphosphonates are associated with gastrointestinal toxicity, including dyspepsia, abdominal pain, gastritis, and esophagitis.[48,50–52] A systematic review[53] of 14 studies assessing the use of oral bisphosphonates for the treatment of osteoporosis found that concern over adverse side effects contributed to suboptimal patient compliance and/or persistence with therapy.

Because oral bisphosphonates have low bioavailability and maximal dosing is limited by the risk of gastrointestinal adverse effects, compliance with complicated dosing regimens is a critical requirement to ensure bioavailability and achieve efficacy.[46] These drugs must be taken with plain water, on an empty stomach after an overnight fast, up to an hour before eating or ingesting other liquids or medications; patients must remain upright for 30–60 minutes after dosing.[45,46] More recent formulations allow for weekly or monthly oral dosing[47,54,55]; however, regardless of the frequency of dosing, the strict dosing regimen remains a burden to patients. Evidence indicates that inconvenient dosing is a primary reason for lack of compliance and patient dissatisfaction with oral bisphosphonates.[56,57]

Intravenous bisphosphonates, including ibandronate and zoledronic acid, have been approved more recently as a treatment alternative for postmenopausal osteoporosis. Although their increased potency allows for more prolonged suppression of bone turnover and longer dosing intervals, intravenous bisphosphonates are generally more expensive than the oral formulations and are sometimes associated with transient flu-like symptoms (acute-phase reactions) and self-limited myalgia.[43,46,58,59]

Hormone therapy

Hormone therapy (estrogen monotherapy or combined estrogen/progestin therapy) is approved in the United States for prevention of postmenopausal osteoporosis, although the primary indication is for treatment of moderate to severe menopausal symptoms (i.e., vasomotor symptoms, vaginal atrophy).[1] Hormone therapy has been shown to effectively reduce the risk of hip, vertebral, and other fractures (approximately 30%–40% relative to placebo).[60–62] Discontinuation of estrogen therapy has been associated with accelerated bone loss, suggesting that long-term, continuous use is necessary to achieve efficacy.[63]

Results from two large, prospective clinical studies suggest that long-term estrogen-based therapy may be associated with an increased risk of adverse health outcomes, such as

stroke and venous thromboembolic events.[60,64–66] A small but significant increase in breast cancer risk was seen in women receiving combined estrogen/progestin therapy in the Women's Health Initiative (WHI) study[64]; in contrast, the use of estrogen therapy alone in hysterectomized women was associated with a 23% lower incidence of invasive breast cancer compared with placebo ($p = 0.06$), a finding that did not reach statistical significance.[60] Based on these findings, many international and national organizations have issued a recommendation that women use hormone therapy only at the lowest effective dose for the minimum length of time based on treatment goals and after careful consideration of the associated risks and benefits.[1,67]

Raloxifene

Raloxifene is a selective estrogen receptor modulator (SERM) approved for the prevention and treatment of postmenopausal osteoporosis. Raloxifene has been shown to reduce vertebral fracture risk by approximately 30%–50% relative to placebo in postmenopausal women with osteoporosis.[68–70] Treatment with raloxifene has not demonstrated significant reductions in the incidence of fractures at the hip or other nonvertebral sites.

Clinical studies[69,71–73] have shown that treatment with raloxifene decreases the risk of invasive breast cancer by 50%–80% relative to placebo, which is similar to the risk reduction observed with tamoxifen. Raloxifene has been shown to significantly increase the risk of venous thromboembolic events,[68,69,71,72,74] and results of the Raloxifene Use for The Heart (RUTH) study[72] demonstrated a 49% increase in the incidence of fatal stroke with raloxifene treatment compared with placebo. Raloxifene use is not recommended in women with a previous history of or at high risk for thromboembolic disease or those who are pregnant,[75] and in women at risk for stroke, the risk–benefit balance should be carefully considered. Raloxifene is also associated with an increased incidence of vasomotor symptoms (ie, hot flashes) and leg cramps.[68,69]

Because clinical data on reductions in fracture risk with raloxifene therapy are not as extensive as those for bisphosphonates, and considering the potential for vasomotor symptoms, venous thromboembolic events, and increased risk for fatal stroke in high-risk populations, raloxifene for postmenopausal osteoporosis is generally considered as a second-line therapy following poor tolerability with first-line agents.[75]

Salmon calcitonin

Salmon calcitonin is approved for the treatment of postmenopausal osteoporosis. In a study of postmenopausal women with osteoporosis, intranasal salmon calcitonin 200 IU/day was shown to reduce the risk of new vertebral fractures by 33% relative to placebo; however, significant reductions in fracture risk were not seen at doses of 100 or 400 IU/day.[76] A significant increase in BMD was observed with the 400 IU/day dose, but no significant effect on hip BMD or nonvertebral fracture risk was noted at any dose. Intranasal salmon calcitonin is associated with an increased incidence of mild to moderate rhinitis (defined as nasal congestion, nasal discharge, or sneezing).[76,77] Because of its relatively low potency compared with other available treatment options, it is generally reserved for osteoporotic women who are unwilling or unable to take other osteoporosis agents.[1,78]

Parathyroid hormone

Teriparatide (human recombinant parathyroid hormone 1–34) administered by daily subcutaneous injection has been shown to stimulate bone formation and resorption, increase BMD, and reduce the risk of vertebral fractures by 65%–69% and nonvertebral fractures by 35%–40% relative to placebo.[79] In a comparative study[80] with alendronate, teriparatide was associated with significantly greater increases in lumbar spine BMD ($p < 0.001$) and a significantly lower incidence of nonvertebral fractures ($p < 0.05$). Teriparatide is associated with an increased incidence of nausea, dizziness, and leg cramps.[79,80] A maximum treatment duration of 2 years is recommended because of limited evidence of efficacy beyond 2 years and preclinical studies showing the development of osteosarcoma in rats.[81] Teriparatide is considerably more expensive than other available osteoporosis agents and is indicated for postmenopausal women and men with osteoporosis who are at high risk for fractures, including those with a history of osteoporotic fracture, very low BMD (i.e., T-score < -3.0), or multiple risk factors for fracture or those who have failed or shown intolerance to previous osteoporosis therapy.[81,82]

It is not known if any of these agents used to reduce fracture risk in women with postmenopausal osteoporosis is more or less effective than any of the others because no randomized head-to-head clinical trial comparing agents—with fractures as the primary end point—has been completed.[83]

Strontium ranelate

Strontium, at low doses, reduces bone resorption and increases bone formation in healthy animals receiving a normal calcium diet. Administration of strontium to ovariectomized rats has been shown to prevent bone loss associated with estrogen deficiency, presumably by decreasing bone resorption. Findings in other models of osteopenia indicate an increase in bone formation with strontium.[84] The results of *in vitro* studies suggest that this may be the result of strontium's role in influencing bone cell recruitment and function.

In a phase II study[85] of postmenopausal women with osteoporosis ($N = 353$), strontium ranelate 2 g/day demonstrated significantly greater increases in lumbar spine BMD at 12 and 24 months compared with placebo. The proportion of subjects experiencing a new vertebral fracture during the second year of treatment was reduced by 44% for strontium ranelate 2 g/day vs. placebo. In a separate study,[86] strontium ranelate 1 g/day demonstrated significant increases in lumbar spine and femoral neck BMD at 2 years compared with placebo.

In the Treatment of Peripheral Osteoporosis study,[87] more than 5000 women with postmenopausal osteoporosis received treatment with strontium ranelate 2 g/day or placebo for 3 years. Compared with placebo, strontium ranelate reduced the incidence of vertebral fractures by 45% at 1 year and 39% at 3 years ($p < 0.001$ for both). Also, the risk of nonvertebral fractures was reduced by 16% with strontium ranelate vs. placebo ($p = 0.04$). Although the risk of hip fracture was reduced by 15%, this was not significantly different from placebo. After the first 3 months of treatment, nausea and diarrhea were more frequent with strontium ranelate treatment than with placebo, but this difference was not apparent thereafter. Findings from a separate study[88] in a comparable (but smaller) population demonstrated similar outcomes. Strontium ranelate is marketed in Europe, Australia, and some other countries but is not yet available in the

United States. It is provided as granules that must be suspended in plain water and consumed immediately at least 2 hours after eating (ideally at bedtime).[85–88]

Poor Compliance with Therapy and Impact on Clinical Outcomes

Despite the availability of numerous treatment options for osteoporosis, persistence with therapy remains suboptimal.[89] A systematic review[53] of the literature found that the average duration of therapy (i.e., persistence) with osteoporosis treatments, primarily bisphosphonates, was generally <1 year. Although persistence with bisphosphonate therapy has been shown to be greater with less frequent dosing (i.e., weekly vs. daily regimen), the overall proportion of patients continuing therapy remains low.[53,90] Results of a survey[90] of women receiving bisphosphonate therapy in the United States, France, and the United Kingdom demonstrated that the 44% of women on the weekly regimen (in the United States) persisted with treatment for 12 months compared with 32% of women on the daily regimen ($p < 0.001$).

Evidence indicates that raloxifene may be associated with lower rates of treatment discontinuation compared with bisphosphonates.[57,91] In a study[57] of postmenopausal Asian women, the 12-month completion rate for daily treatment with either alendronate or risedronate was significantly lower than that with raloxifene (37.5% vs. 50.2%, $p < 0.001$). Results of a Spanish study[91] that evaluated daily therapy with raloxifene or alendronate over a 1-year period also showed significantly higher compliance rates in patients receiving raloxifene vs. alendronate (68.7% vs. 54.0%, $p < 0.001$). In both studies, women taking raloxifene reported greater satisfaction with treatment compared with those taking bisphosphonates ($p < 0.01$).[57,91] Discontinuation rates for women taking hormone therapy appear to be generally similar to or greater than that for women taking bisphosphonates or raloxifene.[89]

Poor persistence with treatment may be associated with smaller decreases in bone turnover, smaller increases in BMD, and a higher risk of fracture and disability.[92] Poor long-term compliance may lead to increased healthcare costs and substantially reduced quality of life, as the likelihood of fractures is increased.[92–94] A recent study[95] showed that noncompliant users of bisphosphonate therapy were 50% more likely to sustain an osteoporotic fracture than were compliant users. The results of a claims database study[96] assessing alendronate and risedronate therapy in women ≥45 years demonstrated that those who were compliant with therapy over a 24-month period had a 21% reduction in the incidence of fractures compared with those who were not adherent to treatment ($p < 0.001$). The largest reduction in risk was noted for hip fractures (30% relative to nonadherent patients). Persistence with therapy (defined as a prescription refill gap of ≤30 days) was associated with a significant reduction in the incidence of all, vertebral, hip, and wrist fractures.[97] An analysis[98] of data from another health insurance database demonstrated that compliance with bisphosphonate or raloxifene therapy for 1 year significantly reduced the risk of hip and vertebral fractures by 60% and 40%, respectively. This effect of compliance on the effectiveness of osteoporosis therapies mirrors that observed with other chronic diseases. For instance, in a meta-analysis[99] of 21 studies evaluating a range of chronic diseases (including cardiovascular diseases, HIV, and diabetes), good compliance with treatment was associated with a 44% decrease in mortality risk.

The reasons for noncompliance with therapy are variable and dependent on the patient and clinical setting. Medication tolerability may play a key role in persistence with therapy.[4] In a study[100] that analyzed dispensed prescriptions for osteoporosis medications in women ≥55 years, there was a significant association between frequency of gastrointestinal adverse events (measured by the concomitant use of selected medications) and decreased persistence with bisphosphonate therapy. In another study,[91] a significantly greater percentage of women treated with alendronate (9.9%) vs. raloxifene (3.4%) experienced gastrointestinal adverse events that led to study withdrawal ($p < 0.001$). Poor compliance with oral bisphosphonates has also been associated with the inconvenience and complexity of the dosing regimen.[53,57] Intravenous administration of bisphosphonates may improve compliance in patients who have trouble with the frequent dosing or gastrointestinal intolerance associated with oral bisphosphonates.[101] Safety concerns are the most commonly cited reason for noncompliance with hormone therapy.[89]

Patients may also fail to continue an osteoporosis medication because they cannot "feel" a benefit or observe evidence of a response to therapy, do not believe their diagnosis, or have a limited understanding of fracture risk.[4,53,89] An analysis[102] of pharmacy claims data showed that patients were more likely to remain on treatment if they had received BMD testing before and after initiation of therapy or had experienced a fracture before and after starting therapy. Patients residing in nursing homes were also more likely to continue treatment, perhaps because of the staff's involvement in drug administration and monitoring. Sometimes, distrust of the pharmaceutical industry or misconceptions regarding the risk of very rare events, such as osteonecrosis of the jaw with bisphosphonates,[103] are factors in patients failing to begin or continue therapy.

The lack of an observed change in BMD with antiresorptive therapy does not necessarily indicate treatment failure, as a key determinant of BMD change is the baseline remodeling rate.[104] Individuals with high baseline remodeling rates generally have greater increases in BMD with therapy than those with low baseline remodeling rates.[104] Although fracture risk may be reduced in both cases,[104] a small increase in BMD may be discouraging and cause a patient to discontinue therapy. Technical errors in the use of dual energy x-ray absorptiometry (DXA) technology (e.g., failure to maintain proper calibration of DXA system, improper patient positioning, mislabeling of scans) can also lead to uninformed patient care decisions.[105] Educating physicians on the proper use of DXA and educating physicians and patients alike on the limitations of BMD testing may help to improve patient compliance.[105]

Suppression of biochemical markers of bone turnover (e.g., C-telopeptide and N-telopeptide) can be detected with antiresorptive therapy after 3–6 months and with anabolic therapies after 1–3 months.[27] Short-term determinations of bone turnover markers have been shown to accurately identify individuals responding to therapy and are reliable predictors of the magnitude of change in BMD and fracture risk.[106–108] Thus, measuring bone markers before and after initiation of therapy may help to identify and encourage treatment responders, thereby improving compliance. One study[5] showed that consultation with a nurse 3 months after initiation of treatment enhanced compliance regardless of whether or not

the patient received information about changes in bone turnover markers. This suggests that the opportunity to discuss treatment issues alone may contribute to improved compliance.

New Therapies

Novel SERMs

A number of novel SERMs are currently undergoing clinical development for the prevention and treatment of postmenopausal osteoporosis. SERMs are known to exhibit estrogen receptor agonist and antagonist activity depending on the target tissue. An ideal SERM for postmenopausal osteoporosis would preserve bone mass and reduce the risk of fractures while minimizing adverse effects, particularly endometrial and breast stimulation. Clinical development of several other SERMs previously evaluated for postmenopausal osteoporosis (e.g., idoxifene, levormeloxifene) was discontinued because of adverse uterine effects, particularly increased endometrial thickness.[109–113]

Bazedoxifene. Bazedoxifene is currently in late-stage clinical development for the prevention and treatment of postmenopausal osteoporosis.[114] In preclinical studies,[115–118] bazedoxifene demonstrated bone-sparing effects and had a favorable impact on the lipid profile without evidence of endometrial or breast stimulation. In rodent models, treatment with bazedoxifene had positive effects on BMD and bone histology and strength and reduced total cholesterol levels. In addition, bazedoxifene was found to inhibit 17β-estradiol–induced and raloxifene-induced increases in uterine wet weight. Bazedoxifene treatment also antagonized 17β-estradiol–induced proliferation of MCF-7 human breast cancer cells in a dose-dependent manner. In a 6-month phase II study[119] of healthy postmenopausal women ($N = 497$), bazedoxifene 2.5–40 mg/day showed no significant change in endometrial thickness as measured by transvaginal ultrasound compared with placebo. There was no case of endometrial hyperplasia with any dose of bazedoxifene.

Among the new SERMs in clinical development, bazedoxifene is the first to have reported results from phase III trials. In a 3-year phase III trial ($N = 7492$)[120] that evaluated bazedoxifene in treating postmenopausal women with osteoporosis, the incidence of new vertebral fractures was reduced by 42%, 37%, and 42% with bazedoxifene 20 mg/day, bazedoxifene 40 mg/day, and raloxifene 60 mg/day, respectively, relative to placebo ($p < 0.05$). In a subgroup of women ($n = 1772$) at higher risk for fracture based on known skeletal risk factors (low femoral neck BMD or prevalent vertebral fracture), bazedoxifene 20 mg significantly reduced the risk of nonvertebral fracture relative to placebo by 50% ($p = 0.02$) and raloxifene 60 mg by 44% ($p = 0.05$). Bazedoxifene was generally well tolerated, with no evidence of endometrial or breast stimulation.[120–122]

In a 2-year phase III study[123] of postmenopausal women with normal or low bone mass ($N = 1583$), treatment with bazedoxifene 10, 20, and 40 mg/day and raloxifene 60 mg/day was shown to prevent bone loss, whereas placebo was associated with a significant loss of BMD at all skeletal sites. Of note, this loss of BMD in placebo-treated women occurred despite daily supplementation with elemental calcium (600 mg). Significant reductions in serum osteocalcin and C-telopeptide levels from baseline and relative to placebo with bazedoxifene and raloxifene treatment were observed as early as 3 months and sustained through study end ($p < 0.001$). No adverse effects on the endometrium or breast were noted with bazedoxifene treatment.[123,124] There were no diagnoses of endometrial hyperplasia or endometrial carcinoma in bazedoxifene-treated subjects. Bazedoxifene did not increase the incidence of breast cancer or breast pain compared with placebo.

Lasofoxifene. Lasofoxifene is undergoing clinical investigation for the prevention and treatment of postmenopausal osteoporosis and for the treatment of vaginal atrophy. In preclinical studies of rodent models, lasofoxifene was shown to prevent bone loss, preserve bone strength, and reduce total cholesterol levels.[125,126] Lasofoxifene also demonstrated a low potential for vaginal or uterine tissue proliferation in immature rats.[127] In a study[128] of surgically postmenopausal cynomolgus monkeys, lasofoxifene was shown to preserve BMD and reduce bone turnover.

In a phase II study[107] ($N = 394$) of healthy postmenopausal women, treatment with lasofoxifene 0.017, 0.05, 0.15, and 0.5 mg/day was shown to significantly increase lumbar spine BMD compared with placebo after 1 year ($p < 0.001$). There were no reports of endometrial cancer, hyperplasia, or other abnormal pathology in the study; however, small but statistically significant increases in mean endometrial thickness were observed with all doses of lasofoxifene relative to placebo. In a 2-year phase II trial[129] ($N = 410$), lasofoxifene 0.25 and 1.0 mg/day were associated with significant increases in lumbar spine BMD compared with placebo or raloxifene 60 mg ($p \leq 0.05$) in postmenopausal women. Effects on hip BMD were similar between the lasofoxifene and raloxifene groups. The incidence of hot flashes and leg cramps was comparable in subjects receiving lasofoxifene or raloxifene and higher than that in subjects receiving placebo. Significant increases in mean endometrial thickness were observed with lasofoxifene treatment compared with placebo ($p < 0.001$).

A 3-year, randomized, double-blind, placebo-controlled phase III trial[130] of postmenopausal women with osteoporosis showed that lasofoxifene 0.25 and 0.5 mg/day significantly reduced the risk of vertebral fracture by 31% and 42%, respectively, relative to placebo ($p < 0.002$). Further, the risk of nonvertebral fracture was reduced by 22% with lasofoxifene 0.5 mg/day relative to placebo ($p = 0.02$).[130] Both doses of lasofoxifene were also shown to significantly increase BMD at the spine and femoral neck compared with placebo ($p < 0.001$) and to reduce levels of bone turnover markers.[131] Compared with placebo, however, lasofoxifene was associated with a significant increase in endometrial thickness and rates of endometrial polyps and vaginal bleeding. Further, lasofoxifene treatment increased the number of diagnostic uterine procedures compared with placebo.[132] Also completed is a 2-year phase III study comparing the effects of lasofoxifene, raloxifene, and placebo on BMD response, low-density lipoprotein cholesterol (LDL-C), and vaginal pH and Maturation Index.[133]

Ospemifene. Ospemifene is currently undergoing clinical evaluation for the treatment of vulvar vaginal atrophy and for the prevention and treatment of osteoporosis in postmenopausal women. Ospemifene has been shown to prevent bone loss, preserve bone strength, and reduce total cholesterol

levels in ovariectomized rats; in immature rats, ospemifene demonstrated a dose-dependent increase in uterine wet weight.[134] In phase II studies[135–137] of healthy postmenopausal women, treatment with ospemifene 30, 60, and 90 mg/day was shown to reduce bone turnover; ospemifene had a similar effect on markers of bone resorption and bone formation as raloxifene. Ospemifene was associated with a significant estrogenic effect on the vaginal epithelium, as demonstrated by decreased parabasal cells and increased intermediate and superficial cells on a Papanicolaou test.[136]

Arzoxifene. Arzoxifene was originally developed for the prevention and treatment of breast cancer; however, phase III studies evaluating arzoxifene for estrogen–positive or hormone receptor–positive breast cancer were discontinued early because of evidence from an interim analysis indicating inferiority of arzoxifene relative to tamoxifen for progression-free survival and time to treatment failure.[138] Arzoxifene is also under investigation for the prevention and treatment of postmenopausal osteoporosis. In rodent models,[139,140] treatment with arzoxifene was shown to prevent bone loss, preserve bone strength, and reduce total cholesterol levels without evidence of endometrial stimulation. Arzoxifene is currently under clinical evaluation in ongoing phase III studies[141–143] of osteoporosis prevention and treatment, based on findings from phase I and II studies demonstrating a reduction in bone turnover with arzoxifene.[144–147]

Denosumab. Denosumab (formerly known as AMG 162) is a fully human monoclonal antibody that inhibits the receptor activator of nuclear factor kappa B ligand, a molecule that enhances the differentiation, function, and survival of osteoclasts. Denosumab is administered by subcutaneous injection every 3 or 6 months and has been studied for the treatment of skeletal diseases, such as bone metastases and multiple myeloma,[148] as well as for osteoporosis. In a 2-year phase II study[149,150] of postmenopausal women with osteopenia or osteoporosis ($N = 412$), denosumab treatment was associated with significant increases in BMD at the lumbar spine, hip, and distal radius compared with placebo. These changes were similar to or greater than those seen with once-weekly alendronate, with the most efficacious doses being denosumab 30 mg every 3 months or 60 mg every 6 months. Discontinuation of denosumab for 2 years was associated with almost complete reversal of BMD gains observed during treatment.[151] In contrast, discontinuation of alendronate led to modest decreases in BMD at the lumbar spine; BMD loss at the total hip was more substantial, but the values remained greater relative to baseline.[151] Findings from a 1-year phase III study[152] of postmenopausal women with low bone mass were consistent with those seen in the 2-year phase II study, as denosumab was associated with significantly greater increases in BMD at the lumbar spine, femoral neck, trochanter, and distal radius compared with alendronate. Findings from phase II and III studies have shown that denosumab is generally well tolerated with a reduction in the risk of vertebral, nonvertebral, and hip fractures.[149,150,152,153]

Summary

Osteoporosis is a skeletal disease that increases the risk of fractures, causing increased morbidity, mortality, and impaired quality of life. It represents a significant social and economic burden, particularly in postmenopausal women. Although our understanding of the pathophysiological origins of osteoporosis has improved greatly over the past two decades and effective diagnostic tools and therapeutic agents have been developed, osteoporosis remains an underdiagnosed and undertreated disease. Evidence indicates that even when treatment is initiated, compliance and persistence are poor. Factors that may contribute to poor compliance with therapy include inadequate patient understanding of fracture risk, complexity of dosing for some agents, adverse events with treatment, fear of adverse events, misleading DXA results, and difficulties in assessing the relative benefit and risk of treatment. Promising new agents, now under investigation in clinical trials, have been developed with the goal of simplifying the dosing regimen and enhancing the benefit–risk profile, thereby improving long-term clinical outcomes.

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References

1. North American Menopause Society. Management of osteoporosis in postmenopausal women: 2006 position statement of The North American Menopause Society. Menopause 2006;13:340–367.
2. Iba K, Takada J, Hatakeyama N, et al. Underutilization of antiosteoporotic drugs by orthopedic surgeons for prevention of a secondary osteoporotic fracture. J Orthop Sci 2006;11:446–449.
3. Vestergaard P, Rejnmark L, Mosekilde L. Osteoporosis is markedly underdiagnosed: A nationwide study from Denmark. Osteoporos Int 2005;16:134–141.
4. Downey TW, Foltz SH, Boccuzzi SJ, Omar MA, Kahler KH. Adherence and persistence associated with the pharmacologic treatment of osteoporosis in a managed care setting. South Med J 2006;99:570–575.
5. Clowes JA, Peel NF, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: A randomized controlled trial. J Clin Endocrinol Metab 2004;89:1117–1123.
6. Dennison E, Cooper C. Epidemiology of osteoporotic fractures. Horm Res 2000;54:58–63.
7. Looker AC, Orwoll ES, Johnston CC Jr, et al. Prevalence of low femoral bone density in older U.S. adults from NHANES III. J Bone Miner Res 1997;12:1761–1768.
8. Gajic-Veljanoski O, Sebaldt RJ, Davis AM, et al. Age and drug therapy are key prognostic factors for first clinical fracture in patients with primary osteoporosis. Osteoporos Int 2007;18:1091–1100.
9. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. Osteoporos Int 2005;16(Suppl 2):S3–S7.

10. Melton LJ III, Thamer M, Ray NF, et al. Fractures attributable to osteoporosis: Report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:16–23.
11. Wainwright SA, Marshall LM, Ensrud KE, et al. Hip fracture in women without osteoporosis. J Clin Endocrinol Metab 2005;90:2787–2793.
12. Nguyen TV, Center JR, Eisman JA. Osteoporosis: Underrated, underdiagnosed and undertreated. Med J Aust 2004;180:S18–S22.
13. Delmas PD, van de Langerijt L, Watts NB, et al. Underdiagnosis of vertebral fractures is a worldwide problem: The IMPACT study. J Bone Miner Res 2005;20:557–563.
14. Kamel HK. Secondary prevention of hip fractures among the hospitalized elderly: Are we doing enough? J Clin Rheumatol 2005;11:68–71.
15. Riggs BL, Melton LJI. The worldwide problem of osteoporosis: Insights afforded by epidemiology. Bone 1995;17: 505S–511S.
16. Atik OS, Gunal I, Korkusuz F. Burden of osteoporosis. Clin Orthop Relat Res 2006;443:19–24.
17. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. JAMA 2001;285:320–323.
18. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA III, Berger M. Patients with prior fractures have an increased risk of future fractures: A summary of the literature and statistical synthesis. J Bone Miner Res 2000;15:721–739.
19. Schlaich C, Minne HW, Bruckner T, et al. Reduced pulmonary function in patients with spinal osteoporotic fractures. Osteoporos Int 1998;8:261–267.
20. Silverman SL, Minshall ME, Shen W, Harper KD, Xie S. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: Results from the Multiple Outcomes of Raloxifene Evaluation Study. Arthritis Rheum 2001;44:2611–2619.
21. Bianchi ML, Orsini MR, Saraifoger S, Ortolani S, Radaelli G, Betti S. Quality of life in post-menopausal osteoporosis. Health Qual Life Outcomes 2005;3:78.
22. Silverman SL, Shen W, Minshall ME, Xie S, Moses KH. Prevalence of depressive symptoms in postmenopausal women with low bone mineral density and/or prevalent vertebral fracture: Results from the Multiple Outcomes of Raloxifene Evaluation (MORE) study. J Rheumatol 2007;34: 140–144.
23. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. Osteoporos Int 2000;11:556–561.
24. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ III. Population-based study of survival after osteoporotic fractures. Am J Epidemiol 1993;137:1001–1005.
25. World Health Organization Collaborating Centre for Metabolic Bone Diseases. FRAX™ WHO Fracture Risk Assessment Tool. Available at www.shef.ac.uk/FRAX/ Accessed March 1, 2008.
26. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the U.K. Osteoporos Int 2008;19:385–397.
27. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Available at www.nof.org/professionals/Clinicians_Guide.htm Accessed December 9, 2008.
28. Gronholz MJ. Prevention, diagnosis, and management of osteoporosis-related fracture: A multifactorial osteopathic approach. J Am Osteopath Assoc 2008;108:575–585.
29. Holick MF. The role of vitamin D for bone health and fracture prevention. Curr Osteoporos Rep 2006;4:96–102.
30. National Osteoporosis Foundation. Scientific statement: Updated recommendations for calcium and vitamin D intake. Available at www.nof.org/prevention/calcium_and_ VitaminD.htm Accessed November 18, 2007.
31. Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. N Engl J Med 1990;323:878–883.
32. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337:670–676.
33. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: Confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: The Decalyos II study. Osteoporos Int 2002;13:257–264.
34. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669–683.
35. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): A randomised placebo-controlled trial. Lancet 2005;365:1621–1628.
36. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D_3) for prevention of fractures in primary care. BMJ 2005;330:1003.
37. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: A meta-analysis. Lancet 2007;370:657–666.
38. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls: A meta-analysis. JAMA 2004; 291:1999–2006.
39. Bischoff HA, Stahelin HB, Dick W, et al. Effects of vitamin D and calcium supplementation on falls: A randomized controlled trial. J Bone Miner Res 2003;18:343–351.
40. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res 2000;15: 1113–1118.
41. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: Results of a randomized trial. Am J Clin Nutr 2007;85:1586–1591.
42. Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: The Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab 2000;85:4118–4124.
43. Bobba RS, Beattie K, Parkinson B, Kumbhare D, Adachi JD. Tolerability of different dosing regimens of bisphosphonates for the treatment of osteoporosis and malignant bone disease. Drug Saf 2006;29:1133–1152.
44. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350:1189–1199.
45. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures

in women with postmenopausal osteoporosis: A randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344–1352.
46. Grey A, Reid IR. Differences between the bisphosphonates for the prevention and treatment of osteoporosis. Ther Clin Risk Manag 2006;2:77–86.
47. Chesnut CHI, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19:1241–1249.
48. Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008;CD004523.
49. Wells GA, Cranney A, Peterson J, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008;CD001155.
50. FOSAMAX® (alendronate sodium) tablets and oral solution [package insert]. Whitehouse Station, NJ: Merck & Co., 2007.
51. ACTONEL® (risedronate sodium tablets) [package insert]. Cincinnati, OH: Proctor & Gamble Pharmaceuticals, 2007.
52. BONIVA® (ibandronate sodium) tablets [package insert]. Nutley, NJ: Roche Pharmaceuticals, 2006.
53. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporos Int 2007;18: 1023–1031.
54. Brown JP, Kendler DL, McClung MR, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int 2002;71: 103–111.
55. Reginster JY, Adami S, Lakatos P, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis 2006;65:654–661.
56. Boonen S, Vanderschueren D, Venken K, Milisen K, Delforge M, Haentjens P. Recent developments in the management of postmenopausal osteoporosis with bisphosphonates: Enhanced efficacy by enhanced compliance. J Intern Med 2008;264:315–332.
57. Pasion EG, Sivananthan SK, Kung AW, et al. Comparison of raloxifene and bisphosphonates based on adherence and treatment satisfaction in postmenopausal Asian women. J Bone Miner Metab 2007;25:105–113.
58. Reid IR, Brown JP, Burckhardt P, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med 2002;346:653–661.
59. Delmas PD, Adami S, Strugala C, et al. Intravenous ibandronate injections in postmenopausal women with osteoporosis: One-year results from the dosing intravenous administration study. Arthritis Rheum 2006;54:1838–1846.
60. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701–1712.
61. Cauley JA, Seeley DG, Ensrud K, Ettinger B, Black D, Cummings SR. Estrogen replacement therapy and fractures in older women. Study of Osteoporotic Fractures Research Group. Ann Intern Med 1995;122:9–16.
62. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: The Women's Health Initiative randomized trial. JAMA 2003;290:1729–1738.
63. Greenspan SL, Emkey RD, Bone HG, et al. Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2002;137:875–883.
64. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–333.
65. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002;288:49–57.
66. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002;288:58–66.
67. Kleerekoper M. Osteoporosis prevention and therapy: Preserving and building strength through bone quality. Osteoporos Int 2006;17:1707–1715.
68. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: Four-year results from a randomized clinical trial. J Clin Endocrinol Metab 2002;87: 3609–3617.
69. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: Results from a 3-year randomized clinical trial. JAMA 1999;282:637–645.
70. Seeman E, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Anti-vertebral fracture efficacy of raloxifene: A meta-analysis. Osteoporos Int 2006;17:313–316.
71. Barrett-Connor E, Cauley JA, Kulkarni PM, Sashegyi A, Cox DA, Geiger MJ. Risk-benefit profile for raloxifene: 4-year data from the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. J Bone Miner Res 2004; 19:1270–1275.
72. Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006;355:125–137.
73. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs. raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006;295:2727–2741.
74. Mosca L, Grady D, Barrett-Connor E, et al. Effect of raloxifene on stroke and venous thromboembolism according to subgroups in postmenopausal women at increased risk of coronary heart disease. Stroke 2009;40:147–155.
75. Bushardt RL, Turner JL, Ragucci KR, Askins DG Jr. Nonestrogen treatments for osteoporosis: An evidence-based review. JAAPA 2006;19:25–30.
76. Chesnut CH III, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: The Prevent Recurrence of Osteoporotic Fractures study. PROOF Study Group. Am J Med 2000;109:267–276.
77. Ellerington MC, Hillard TC, Whitcroft SI, et al. Intranasal salmon calcitonin for the prevention and treatment of postmenopausal osteoporosis. Calcif Tissue Int 1996;59:6–11.
78. MIACALCIN® (calcitonin-salmon) nasal spray [package insert]. Huningue, France: Novartis Pharma S.A.S., 2006.

79. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–1441.
80. Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1–34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 2002;87:4528–4535.
81. FORTEO™ teriparatide (rDNA origin) injection 750 mcg/3 mL [package insert]. Indianapolis, IN: Eli Lilly, 2007.
82. Hodsman AB, Bauer DC, Dempster DW, et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: A review of the evidence and suggested guidelines for its use. Endocr Rev 2005;26:688–703.
83. Seeman E. Preventing fractures—How good are we really? Nat Clin Pract Endocrinol Metab 2006;2:606–607.
84. Marie PJ, Ammann P, Boivin G, Rey C. Mechanisms of action and therapeutic potential of strontium in bone. Calcif Tissue Int 2001;69:121–129.
85. Meunier PJ, Slosman DO, Delmas PD, et al. Strontium ranelate: Dose-dependent effects in established postmenopausal vertebral osteoporosis—A 2-year randomized placebo controlled trial. J Clin Endocrinol Metab 2002;87:2060–2066.
86. Reginster JY, Meunier PJ. Strontium ranelate phase 2 dose-ranging studies: PREVOS and STRATOS studies. Osteoporos Int 2003;14 (Suppl 3):S56–S65.
87. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005;90:2816–2822.
88. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004;350:459–468.
89. Papaioannou A, Kennedy CC, Dolovich L, Lau E, Adachi JD. Patient adherence to osteoporosis medications: Problems, consequences and management strategies. Drugs Aging 2007;24:37–55.
90. Cramer JA, Lynch NO, Gaudin AF, Walker M, Cowell W. The effect of dosing frequency on compliance and persistence with bisphosphonate therapy in postmenopausal women: A comparison of studies in the United States, the United Kingdom, and France. Clin Ther 2006;28:1686–1694.
91. Turbi C, Herrero-Beaumont G, Acebes JC, et al. Compliance and satisfaction with raloxifene versus alendronate for the treatment of postmenopausal osteoporosis in clinical practice: An open-label, prospective, nonrandomized, observational study. Clin Ther 2004;26:245–256.
92. Cramer JA, Silverman S. Persistence with bisphosphonate treatment for osteoporosis: Finding the root of the problem. Am J Med 2006;119:S12–S17.
93. Silverman SL, Gold DT. Compliance and persistence with osteoporosis therapies. Curr Rheumatol Rep 2008;10:118–122.
94. Moro-Alvarez MJ, Diaz-Curiel M. Risedronate once monthly: A potential new regimen for the treatment of postmenopausal osteoporosis. Clin Interventions Aging 2008;3:227–232.
95. Penning-van Beest FJA, Erkens JA, Olson M, Herings RMC. Loss of treatment benefit due to low compliance with bisphosphonate therapy. Osteoporos Int 2008;19:511–517.
96. Siris ES, Harris ST, Rosen CJ, 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.
97. Gold DT, Martin BC, Frytak JR, Amonkar MM, Cosman F. A claims database analysis of persistence with alendronate therapy and fracture risk in post–menopausal women with osteoporosis. Curr Med Res Opin 2007;23:585–594.
98. McCombs JS, Thiebaud P, Laughlin-Miley C, Shi J. Compliance with drug therapies for the treatment and prevention of osteoporosis. Maturitas 2004;48:271–287.
99. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ 2006;333:15.
100. Penning-van Beest FJ, Goettsch WG, Erkens JA, Herings RM. Determinants of persistence with bisphosphonates: A study in women with postmenopausal osteoporosis. Clin Ther 2006;28:236–242.
101. Strampel W, Emkey R, Civitelli R. Safety considerations with bisphosphonates for the treatment of osteoporosis. Drug Saf 2007;30:755–763.
102. Solomon DH, Avorn J, Katz JN, et al. Compliance with osteoporosis medications. Arch Intern Med 2005;165:2414–2419.
103. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2007;22:1479–1491.
104. Seeman E. Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy? Bone 2007;41:308–317.
105. Lewiecki EM, Lane NE. Common mistakes in the clinical use of bone mineral density testing. Nat Clin Pract Rheumatol 2008;4:667–674.
106. Camacho PM, Lopez NA. Use of biochemical markers of bone turnover in the management of postmenopausal osteoporosis. Clin Chem Lab Med 2008;46:1345–1357.
107. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J Bone Miner Res 2003;18:1051–1056.
108. Ravn P, Hosking D, Thompson D, et al. Monitoring of alendronate treatment and prediction of effect on bone mass by biochemical markers in the early postmenopausal intervention cohort study. J Clin Endocrinol Metab 1999;84:2363–2368.
109. Fleischer AC, Wheeler JE, Yeh IT, Kravitz B, Jensen C, MacDonald B. Sonographic assessment of the endometrium in osteopenic postmenopausal women treated with idoxifene. J Ultrasound Med 1999;18:503–512.
110. Alexandersen P, Riis BJ, Stakkestad JA, Delmas PD, Christiansen C. Efficacy of levormeloxifene in the prevention of postmenopausal bone loss and on the lipid profile compared to low dose hormone replacement therapy. J Clin Endocrinol Metab 2001;86:755–760.
111. Goldstein SR, Nanavati N. Adverse events that are associated with the selective estrogen receptor modulator levormeloxifene in an aborted phase III osteoporosis treatment study. Am J Obstet Gynecol 2002;187:521–527.
112. Smith Kline Beecham drops idoxifene for osteoporosis. SCRIP 1999;2431:21.
113. Novo Nordisk drops levormeloxifene. SCRIP 1998;2374:18.
114. Lewiecki EM. Bazedoxifene and bazedoxifene combined with conjugated estrogens for the management of post-

menopausal osteoporosis. Expert Opin Investig Drugs 2007;16:1663–1672.
115. Gruber C, Gruber D. Bazedoxifene (Wyeth). Curr Opin Investig Drugs 2004;5:1086–1093.
116. Komm BS, Lyttle CR. Developing a SERM: Stringent preclinical selection criteria leading to an acceptable candidate (WAY-140424) for clinical evaluation. Ann NY Acad Sci 2001;949:317–326.
117. Komm BS, Kharode YP, Bodine PV, Harris HA, Miller CP, Lyttle CR. Bazedoxifene acetate: A selective estrogen receptor modulator with improved selectivity. Endocrinology 2005;146:3999–4008.
118. Marín F, Barbancho MC. Clinical pharmacology of selective estrogen receptor modulators (SERMs). In: Sanchez AC, Alsina JCi, Dueñas-Díez JL, eds. Selective estrogen receptor modulators. A new brand of multitarget drugs. New York: Springer, 2006:49–65.
119. Ronkin S, Northington R, Baracat E, et al. Endometrial effects of bazedoxifene acetate, a novel selective estrogen receptor modulator, in postmenopausal women. Obstet Gynecol 2005;105:1397–1404.
120. Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo- and active-controlled clinical trial. J Bone Miner Res 2008;23:1923–1934.
121. Adachi JD, Chesnut CH, Brown JP, et al. Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis: Results from a 3-year, randomized, placebo- and active-controlled clinical trial. J Bone Miner Res 2007;22:S460 [Abstract W385].
122. Archer DF, Pinkerton JV, Utian W, et al. Bazedoxifene, a selective estrogen receptor modulator: Effects on the endometrium, ovaries, and breast from a randomized controlled trial in osteoporotic postmenopausal women [published online ahead of print June 10, 2009]. Menopause doi:10.1097/gme.06013e3181a818db.
123. Miller PD, Chines AA, Christiansen C, et al. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-year results of a randomized, double-blind, placebo-, and active-controlled study. J Bone Miner Res 2008;23:525–535.
124. Pinkerton JV, Archer DF, Utian WH, et al. Bazedoxifene effects on the reproductive tract in postmenopausal women at risk for osteoporosis [published online ahead of print June 10, 2009]. Menopause doi:10.1097/gme. 0601ze3181a816be.
125. Ke HZ, Paralkar VM, Grasser WA, et al. Effects of CP-336,156, a new, nonsteroidal estrogen agonist/antagonist, on bone, serum cholesterol, uterus and body composition in rat models. Endocrinology 1998;139:2068–2076.
126. Ke HZ, Foley GL, Simmons HA, Shen V, Thompson DD. Long-term treatment of lasofoxifene preserves bone mass and bone strength and does not adversely affect the uterus in ovariectomized rats. Endocrinology 2004;145:1996–2005.
127. Wang XN, Simmons HA, Salatto CT, Cosgrove PG, Thompson DD. Lasofoxifene enhances vaginal mucus formation without causing hypertrophy and increases estrogen receptor beta and androgen receptor in rats. Menopause 2006;13:609–620.
128. Lees C, Shen V, Brommage R. Effects of lasofoxifene on bone in surgically postmenopausal cynomolgus monkeys. Menopause 2007;14:97–105.
129. McClung MR, Siris E, Cummings S, et al. Prevention of bone loss in postmenopausal women treated with lasofoxifene compared with raloxifene. Menopause 2006;13: 377–386.
130. Cummings SR, Eastell R, Ensrud K, et al. The effects of lasofoxifene on fractures and breast cancer: 3-year results from the PEARL Trial. J Bone Miner Res 2008;23:81 [Abstract 1288].
131. Eastell R, Reid DM, Vukicevic S, et al. The effects of lasofoxifene on bone turnover markers: The PEARL Trial. J Bone Miner Res 2008;23:81 [Abstract 1287].
132. Pfizer Inc. FABLYN® (lasofoxifene tartrate) 0.5 mg tablets. NDA 22-242. Reproductive Health Drugs Advisory Committee Briefing Document, September 8, 2008. Available at www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4381b102-Pfizer.pdf Accessed October 27, 2008.
133. CORAL: Comparison of raloxifene and lasofoxifene—A randomized, blinded study of these drugs and placebo on bone loss. ClinicalTrials.gov Identifier: NCT00163137. Available at www.clinicaltrials.gov/ct/show/NCT00163137?order=3 Accessed April 24, 2008.
134. Qu Q, Zheng H, Dahllund J, et al. Selective estrogenic effects of a novel triphenylethylene compound, FC1271a, on bone, cholesterol level, and reproductive tissues in intact and ovariectomized rats. Endocrinology 2000;141: 809–820.
135. Komi J, Heikkinen J, Rutanen EM, Halonen K, Lammintausta R, Ylikorkala O. Effects of ospemifene, a novel SERM, on biochemical markers of bone turnover in healthy postmenopausal women. Gynecol Endocrinol 2004;18:152–158.
136. Rutanen EM, Heikkinen J, Halonen K, Komi J, Lammintausta R, Ylikorkala O. Effects of ospemifene, a novel SERM, on hormones, genital tract, climacteric symptoms, and quality of life in postmenopausal women: A double-blind, randomized trial. Menopause 2003;10:433–439.
137. Komi J, Lankinen KS, DeGregorio M, et al. Effects of ospemifene and raloxifene on biochemical markers of bone turnover in postmenopausal women. J Bone Miner Metab 2006;24:314–318.
138. Deshmane V, Krishnamurthy S, Melemed AS, Peterson P, Buzdar AU. Phase III double-blind trial of arzoxifene compared with tamoxifen for locally advanced or metastatic breast cancer. J Clin Oncol 2007;25:4967–4973.
139. Ma YL, Bryant HU, Zeng Q, et al. Long-term dosing of arzoxifene lowers cholesterol, reduces bone turnover, and preserves bone quality in ovariectomized rats. J Bone Miner Res 2002;17:2256–2264.
140. Sato M, Turner CH, Wang T, Adrian MD, Rowley E, Bryant HU. LY353381.HCl: A novel raloxifene analog with improved SERM potency and efficacy *in vivo*. J Pharmacol Exp Ther 1998;287:1–7.
141. Gennari L, Merlotti D, Valleggi F, Martini G, Nuti R. Selective estrogen receptor modulators for postmenopausal osteoporosis: Current state of development. Drugs Aging 2007;24:361–379.
142. U.S. National Institute of Health, National Library of Medicine. Effects of arzoxifene on bone mass and the uterus. Available at www.clinicaltrials.gov/ct2/show/NCT00085956 Accessed April 8, 2008.
143. Effects of arzoxifene on bone fractures and incidence of breast cancer. ClinicalTrials.gov Identifier: NCT00088010. Available at www.clinicaltrials.gov/ct/show/NCT00088010 Accessed April 8, 2008.
144. Study comparing arzoxifene with raloxifene in women after menopause with osteoporosis. ClinicalTrials.gov Identifier:

NCT00383422. Available at www.clinicaltrials.gov/ct/show/NCT00383422?order=5 Accessed April 24, 2008.
145. Baselga J, Llombart-Cussac A, Bellet M, et al. Randomized, double-blind, multicenter trial comparing two doses of arzoxifene (LY353381) in hormone-sensitive advanced or metastatic breast cancer patients. Ann Oncol 2003;14:1383–1390.
146. Buzdar A, O'Shaughnessy JA, Booser DJ, et al. Phase II, randomized, double-blind study of two dose levels of arzoxifene in patients with locally advanced or metastatic breast cancer. J Clin Oncol 2003;21:1007–1014.
147. Munster PN, Buzdar A, Dhingra K, et al. Phase I study of a third-generation selective estrogen receptor modulator, LY353381.HCL, in metastatic breast cancer. J Clin Oncol 2001;19:2002–2009.
148. Body JJ, Facon T, Coleman RE, et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res 2006;12:1221–1228.
149. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med 2006;354:821–831.
150. Lewiecki EM, Miller PD, McClung MR, et al. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. J Bone Miner Res 2007;22:1832–1841.
151. Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: A randomized blinded phase 2 clinical trial. Bone 2008;43:222–229.
152. Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mass: A randomized, blinded, phase 3 trial. J Bone Miner Res 2009;24:153–161.
153. Cummings S, Zanchetta J, McClung M, et al. The effects of twice–yearly denosumab on fracture risk in women with osteoporosis. Osteoporos Int 2009;20:516.

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