



Postmenopausal Osteoporosis

Current and Future Treatment Options

Carrie McAdam-Marx, RPh, MS, Joanne LaFleur, PharmD, MSPH,
Carmen Kirkness, MSc, PT, and Carl Asche, PhD

ABSTRACT

Purpose: Postmenopausal osteoporosis (PMO) is a significant health and economic burden on the U.S. Costs related to osteoporosis are approximately \$14 billion per year, driven primarily by fractures. We undertook a review of clinical trial and pharmaco-economic literature related to PMO to summarize efficacy and cost-effectiveness data for current and future pharmaceutical treatment options.

Methods: We searched Medline, International Pharmaceutical Abstracts, Business Source Premier, and *Research Digest* (published by the International Society for Pharmacoeconomics and Outcomes Research) for articles from 1995 to 2006 using osteoporosis-related terms. We selected articles for review if they focused on a PMO population, if they were stratified by sex and age to identify the PMO population, if they reported fracture endpoints, or if they covered U.S. pharmaco-economic data.

Results: Current pharmacotherapy for PMO includes anti-resorptive agents (bisphosphonates, selective estrogen receptor modulators, and calcitonin), which reduce bone turnover, and anabolic agents (parathyroid hormone), which stimulate bone development. Antiresorptive products reduce vertebral fracture rates by 30% to 70% and are cost-effective in preventing fractures in women with osteoporosis and low bone mineral density (BMD) or with a previous fragility fracture. Teriparatide, a parathyroid hormone (PTH) reduces vertebral fracture rates by 65% to 69%, although cost-effectiveness is limited to high-risk patients of advanced age or with very low BMD. Promising products under review include strontium ranelate, available for PMO outside the U.S., and PTH (1-84), an anabolic agent.

Conclusion: Antiresorptive agents are cost-effective for preventing fractures in women with osteoporosis, but they might not offer enough protection in high-risk populations. Thus, there is a cost-effective place for an anabolic agent in the highest-risk patients. Strontium ranelate and PTH (1-84) may offer additional therapeutic options in preventing fractures in PMO.

INTRODUCTION

Osteoporosis is defined as a disease of the skeletal system, characterized by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue that can lead to enhanced bone fragility and a consequent increase in fracture risk.^{1,2} In the U.S., 54% of postmenopausal white women are osteopenic and 30% are osteoporotic.³ A 50-year-old white woman has a 40% lifetime probability of a hip, spine, or forearm fracture.² The estimated one-year direct and indirect costs of osteoporosis for those 45 years of age and older are \$14 billion.⁴ Costs are

primarily driven by hospitalizations related to fractures resulting from osteoporosis; costs range from \$15,500 for any osteoporosis-related hospitalization to \$17,383 for an osteoporosis fracture-related admission.^{5,6}

In the absence of a fragility fracture, a diagnosis of osteoporosis can be made with a measurement of BMD. The expression of BMD, compared with the reference mean, is known as the T-score.⁷ According to World Health Organization (WHO) guidelines, osteoporosis is indicated by BMD that is 2.5 standard deviations (SDs) or more below the reference mean for a young adult female. Thus, osteoporosis would be defined as a T-score of -2.5 or below (e.g., -3.0).² A T-score above -2.5 (e.g., -1.0) would not be defined as osteoporosis in the absence of a fragility fracture.

Although low BMD is an important diagnostic criterion for osteoporosis, it is also an independent risk factor for fracture. Additional independent risk factors include low weight or low body mass index (BMI), advancing age, corticosteroid use, a history of fractures, a family history of hip fractures, and secondary osteoporosis associated with disorders such as rheumatoid arthritis (Table 1).⁸⁻²⁸ Lifestyle factors, including current smoking, excessive alcohol consumption of more than 2 units (approximately two drinks of alcohol) per day, have also been independently associated with osteoporotic fractures.^{29,30}

The presence of multiple risk factors substantially increases the overall rate of fractures. For example, the incidence of fractures for patients with zero to two independent risk factors, in addition to a low BMD T-score, is 2.6 hip fractures per 1,000. The rate of hip fracture for those with low BMD and five or more additional risk factors is 27.3 per 1,000.¹¹ WHO has identified the cumulative role of risk factors for fractures and has generated a model estimating the 10-year probability of an osteoporotic fracture based on these risk factors.³¹

A number of therapeutic options are available for treating bone loss and, ultimately, for avoiding fractures, and several promising agents are in development. More recent evidence has advanced our scientific understanding of why these agents help improve bone mass and structural quality, thus preventing fractures, and this new information is influencing current treatment opinions. However, new therapeutic alternatives and philosophies should consider pharmaco-economic data that incorporate risk reduction in terms of baseline risks to ensure that the products used are cost-effective. New approaches and economic considerations could change the way health care organizations shape their formularies and recommended treatment guidelines for postmenopausal osteoporosis (PMO).

Our objective was to conduct a thorough review of recent clinical trial and pharmaco-economic literature related to osteoporosis.

Disclosure: NPS Pharmaceuticals provided funding for this research.

Carrie McAdam-Marx and Carmen Kirkness are Research Associates, Joanne LaFleur is Research Assistant Professor, and Carl Asche is Research Associate Professor, all at the University of Utah Pharmacotherapy Outcomes Research Center in Salt Lake City, Utah.

Postmenopausal Osteoporosis: Treatment Options

sis pharmacotherapy. This article summarizes the literature regarding efficacy, safety, and economic data for current and future pharmaceutical treatments specifically related to PMO, which represents a significant portion of the total population with osteoporosis.

METHODS

We performed a librarian-conducted Medline search to identify literature on the efficacy and economics of PMO treatment from 1995 to 2006. Other databases included International Pharmaceutical Abstracts; Business Source Premier; and *Research Digest*, from the International Society for Pharmacoeconomics and Outcomes Research. We also used package inserts for individual treatment options.

RESULTS

Pharmacological treatment recommendations to prevent fractures in women with PMO include:

- antiresorptive agents: bisphosphonates, selective estrogen receptor modulators (SERMs), and calcitonin.
- bone anabolic agents: the parathyroid hormone (PTH) therapeutic class.^{2,32-35}

Until evidence of risks of cardiovascular disease and breast cancer associated with hormone replacement therapy (HRT) was published in 2003, HRT had been recommended for preventing menopause-related bone loss and PMO until evidence of risks of cardiovascular disease and breast cancer associated with HRT was published in 2003. Based on these risks, most guidelines do not broadly recommend HRT for PMO prevention; instead, they suggest that the risks and benefits of HRT be carefully weighed for each patient.^{2,32,33}

PHARMACOTHERAPY REVIEW

In this article, we discuss products for which an indication has been approved by the Food and Drug Administration (FDA), or when clinical trial data support their use for PMO, and when there is a focus on clinical efficacy, as measured by a reduced risk of fracture. Approved indications, recommended dosages, and side effects are summarized in Table 2. Table 3 presents an overview of clinical trials reporting efficacy for these products.

Multiple products are in clinical development in the U.S. for use in PMO, such as:

- zoledronic acid (Reclast, Novartis), a bisphosphonate.
- two SERMs (one agent, bazedoxifene, has received an approvable letter from the FDA).
- another form of human PTH (1-84), or "full-length" PTH.
- two PTH intranasal agents.
- an oral PTH formulation.
- PTH-related protein (PTHrP).
- denosumab (AMG-162, Amgen, a fully human monoclonal antibody that neutralizes the receptor activator of nuclear factor- κ B ligand (RANKL).
- cathepsin K inhibitor, which prevents bone loss while allowing bone formation to continue.

Table 1 Increase in Hip Fracture Risk by Risk Factor

Risk Factor	Increase in Risk*	Reference No.
Age, per 5-year increase	40%–70%	8–15
Prior fracture	50%–200%	9, 11, 13, 14, 16–18, 23
BMD, per SD decrease	30%–85%	10, 19–22, 24
BMI, per SD decrease	12%–31%	14, 15
Weight, below 75 kg	100%	9
Maternal history of fracture	68%–80%	9, 11
Corticosteroid use (current or prior)	42%–342%	25, 26
Rheumatoid arthritis	73%–100%	27, 28
Smoking, current	18%–85%	29
Alcohol, intake more than 2 units (about 2 drinks) per day	33%–72%	30

* Relative risk not adjusted for other risk factors.

BMD = bone mineral density; SD = standard deviation.

- Strontium ranelate, which is available in Europe and promotes bone formation while decreasing bone resorption.

Published phase 2 and 3 studies with fracture endpoints were available for PTH (1-84) and strontium ranelate, and they are thus discussed in this review.

Antiresorptive Agents

Bisphosphonates

Bisphosphonates are antiresorptive agents that inhibit the bone-resorptive activity of osteoclasts, thereby reducing bone turnover and bone loss.^{36,37} Three bisphosphonates have FDA approval for treating and preventing osteoporosis: alendronate (Fosamax, Merck), risedronate (Actonel, Procter & Gamble/Sanofi-Aventis), and ibandronate (Boniva, Roche).³⁸⁻⁴¹ These drugs for PMO are available in oral formulations for daily dosing. Alendronate and risedronate are also available in once-weekly oral formulations, and ibandronate is available in a once-monthly oral formulation. Injectable ibandronate is available for quarterly administration.

Bridging studies were conducted for intermittent oral and injectable dosage forms of alendronate, risedronate, and ibandronate to establish equivalency to daily dosage formulations based on BMD outcomes.⁴²⁻⁴⁶ However, because these studies did not include fracture outcomes, they are not discussed in this article.

Etidronate disodium (Didronel, Procter & Gamble) and zoledronic acid are available in the U.S. Although they show evidence of fracture efficacy in PMO, they are not approved for osteoporosis.^{47,48} Etidronate, indicated for Paget's disease, is approved for osteoporosis outside the U.S. An injectable agent, zoledronic acid is approved for hypercalcemia of malignancy, bone metastases of solid tumors, and Paget's disease.

The most common adverse drug events (ADEs) associated with alendronate, risedronate, and ibandronate are upper gastrointestinal (GI) side effects such as dysphagia, esophagitis, esophageal ulcers, and gastric ulcers.³⁸⁻⁴¹ A rare but recently publicized ADE occurring with all bisphosphonates is osteonecrosis of the jaw (ONJ).^{38-40,47-49} This uncommon ADE has been reported most frequently with zoledronic acid and

Postmenopausal Osteoporosis: Treatment Options

Table 2 Indications and Dosing for Products Used in Osteoporosis

Product	Approved Indication	PMO Dose*	Side Effect	Comment
Bisphosphonates				
Alendronate	Prevention and treatment of PMO Osteoporosis in men Glucocorticoid-induced osteoporosis Paget's disease	Prevention: 35 mg q.w., 5 mg q.d. Treatment: 70 mg q.w., 10 mg q.d.	Dysphagia, esophagitis, esophageal ulcer, gastric ulcer	Risk of upper GI adverse events may be greater in women who lie down after taking dose or who do not take with adequate amount of water
Risedronate	Prevention and treatment of PMO Glucocorticoid-induced osteoporosis Osteoporosis in men Paget's disease	5 mg q.d., 35 mg q.w.	Dysphagia, esophagitis, esophageal ulcer, gastric ulcer	Risk of upper GI adverse events may be greater in women who lie down after taking dose or who do not take with adequate amount of water
Ibandronate	Prevention and treatment of PMO	2.5 mg q.d.; 150 mg q.m. 3 mg IV, every 3 months	Dysphagia, esophagitis, esophageal ulcer, gastric ulcer	Risk of upper GI adverse events may be greater in women who lie down after taking dose or who do not take with adequate amount of water
Etidronate	Paget's disease	400 mg/day every 3 months	Headache, gastritis, leg cramps, arthralgia	Approved for use in osteoporosis outside U.S.
Pamidronate	Hypercalcemia of malignancy, Paget's disease, osteolytic bone metastasis of breast cancer, osteolytic lesions of multiple myeloma	30 mg IV over 3 hours every 3 months	Hypertension, headache, musculoskeletal pain, ONJ	Dose and infusion times vary by indication See package insert for details Risk of renal adverse events may be reduced if infused over a longer time
Zoledronic acid	Hypercalcemia of malignancy, bone metastasis of solid tumor, Paget's disease	4 mg IV over 15 minutes for one dose	Musculoskeletal pain, nausea, fever, deteriora- tion in renal function, ONJ	Incidence of renal adverse effects greater with short infusion time (i.e., 5 minutes)
SERMs				
Raloxifene	Prevention and treatment of PMO	60 mg q.d.	Hot flashes, leg cramps	Associated with increased risk of venous thrombosis
Calcitonin				
Calcitonin-salmon	Treatment of PMO	200 IU intranasal q.d. 100 IU SQ q.o.d.	Rhinitis, back pain	Indicated for PMO when HRT is not tolerated or is not acceptable
Parathyroid hormones				
Teriparatide	Treatment of PMO with previous fracture or multiple risk factors	20 mcg SQ q.d.	Leg cramps, dizziness	Associated with osteosarcoma in rats Treatment for more than 2 years not recommended
<p>GI = gastrointestinal; HRT = hormone replacement therapy; IU = International Unit; ONJ = osteonecrosis of the jaw; PMO = postmenopausal osteoporosis; q.d. = daily; q.m. = monthly; q.o.d. = every other day; q.w. = weekly; SERM = selective estrogen receptor modulator; SQ = subcutaneous.</p> <p>* If not approved for PMO, the dose provided is the approved indication.</p> <p>Data from product prescribing information.</p>				

pamidronate (Aredia, Novartis) in cancer patients who have received chemotherapeutic agents or glucocorticoids and who have undergone invasive dental procedures. A few cases have been reported for patients using oral bisphosphonates for PMO or other diagnoses.

Alendronate (Fosamax) and Alendronate/Cholecalciferol (Fosamax Plus D)

The safety and fracture efficacy of alendronate in the treatment of PMO were established with the Alendronate Phase 3 Osteoporosis Treatment Group trials⁵⁰ and the Fracture Intervention Trial (FIT).⁵¹⁻⁵³ Data from the three-year trials were

Postmenopausal Osteoporosis: Treatment Options

Table 3 Efficacy of Treatment in Fracture Prevention in Postmenopausal Osteoporosis*

Product	Dose for Active Arm	Reduction in Fracture Risk	Key/Comment
Bisphosphonates			
Alendronate	5 mg q.d. 24 months, then 10 mg/day 5 mg or 10 mg q.d.	47% (v) ^a 44% (v) ^b NS (nv) ^c 65% (v) ^c	a. postmenopausal women with a prior fracture at 3 years ⁵¹ b. postmenopausal women with no prior fracture at 4 years ⁵² c. trial extension, between treatment years 6 and 10 ⁵⁴
	5 mg or 10 mg q.d. 5 mg, 10 mg q.d.	48% (v) ^d NS (v) ^e	d. postmenopausal women at 3 years ⁵¹ e. trial extension, between treatment years 6 and 10 ⁵⁴
Risedronate	2.5 mg or 5 mg q.d. 2.5 mg or 5 mg q.d.	41% (v) ^f 40% (h) ^g	f. postmenopausal women with a prior fracture at 3 years ⁵⁷ g. postmenopausal women with T-scores of -3.0 to -4.0, + one other risk factor at 3 years ⁵⁸
Ibandronate	2.5 mg q.d. or 20 mg cyclical†	50%–62% (v) ^h	h. postmenopausal women with T-scores below -2.5 and a prior fracture at 3 years ⁶⁰
Etidronate	400 mg days 4–17 of 90-day cycle	NS ⁱ	i. prevention trial in postmenopausal women at 3 years ^{61,62}
Zoledronic acid	5 mg IV over 15 minutes	25% (nv) ^j 41% (h) ^j 70% (v) ^j	j. postmenopausal women with T-scores below -2.5 or below -1.5 and two prior mild or one moderate vertebral fracture ⁶³
SERMs			
Raloxifene	60 mg q.d.	40% (v) ^k 30% (v) ^l NS ^m	k. postmenopausal women with T-scores below -2.5 with no prior fracture at 3 years ⁶⁵ l. postmenopausal women with T-scores of below -2.5, with a prior fracture at 3 years ⁶⁵ m. extension trial, years 4 to 8 ⁶⁷
Calcitonin			
Calcitonin-salmon	200 IU intranasal q.d.	33% (v) ⁿ	n. postmenopausal women at 5 years ⁶⁸
Parathyroid hormone			
Teriparatide	20 mcg	65% (v) ^o 53% (nv) ^o	o. postmenopausal women with a prior vertebral fracture at 17 to 19 months ⁷⁰
<p>h = hip; IU = International Units; NS = not significant; nv = nonvertebral; q.d., = daily; q.m. = monthly; q.w. = weekly; v = vertebral. * All were randomized, placebo-controlled trials of fracture reduction with treatment versus placebo. † Once daily for 12 doses every 3 months.</p>			

combined to determine a reduced fracture risk.⁵⁰ A total of 994 postmenopausal women were randomly assigned to receive placebo or alendronate 5 mg, 10 mg, or 20 mg/day. The risk of vertebral fractures in women treated with alendronate, compared with placebo, was reduced by 48% ($P < 0.05$). A 12% reduction in nonvertebral fracture was observed but was not significant.

Three trial extensions provided a total study period of 10 years.⁵⁴ The 5-mg and 10-mg treatment groups continued with the same dose after the third year; the 20-mg group received 5 mg/day for the fourth and fifth years and then placebo for years six to 10. Fracture data from years six to 10 were evaluated for 228 women. These patients were observed for the full 10 years. During this five-year extension period, the proportion of women with vertebral fractures did not differ between those who discontinued therapy (6.6%), the 5-mg treatment group (13.9%), or the 10-mg treatment group (5%).

FIT was a randomized, controlled, double-blinded clinical trial of postmenopausal women with low BMD. The study

authors compared placebo and alendronate 5 mg/day for 24 months, followed by 10 mg/day for the third year. In a three-year analysis of the 2,027 postmenopausal women with a history of fractures, alendronate was associated with a 47% lower risk of new vertebral fractures, compared with placebo ($P < 0.001$).⁵¹ Women treated with alendronate also had a lower risk of any fracture, compared with the placebo group, but the difference did not reach statistical significance.

In a four-year analysis of 4,432 postmenopausal women participating in FIT who did not have a previous fracture, the risk of vertebral fracture was reduced by 44% ($P = 0.002$); the trend toward lower risk of any nonvertebral fracture did not reach significance.⁵² The reduction in fracture risk was observed in women with baseline hip BMD T-scores below or equal to -2.5 (e.g., -3.0). In this low BMD group, treatment was associated with a 50% lower risk of vertebral fractures and a 36% lower risk of any fracture, compared with placebo ($P < 0.001$). Fracture risk reduction was not statistically significant for women with base-

Postmenopausal Osteoporosis: Treatment Options

line hip BMD T-scores above -2.5 .

The Fracture Intervention Trial Long-Term Extension (FLEX) study evaluated the effects of discontinuing alendronate after five years of treatment compared with 10 years of treatment.⁵⁵ In this study, 1,099 alendronate participants from the FIT trial were randomly assigned to receive alendronate 5 mg, alendronate 10 mg, or placebo. After five years, the authors found no significant difference between treated and placebo groups in the risk of nonvertebral fractures (risk ratio [RR] = 1.0; 95% confidence interval [CI], 0.76–1.32) or in the risk of morphometric vertebral fractures (RR = 0.86; 95% CI, 0.60–1.22). However, there was a significant reduction in clinical vertebral fractures with alendronate compared with placebo (RR = 0.45; 95% CI, 0.24–0.85).

Risedronate (Actonel, Actonel with Calcium)

Randomized, placebo-controlled, double-blind studies evaluated the efficacy of risedronate in reducing the incidence of fractures in postmenopausal women in the U.S. In the Vertebral Efficacy with Risedronate study (VERT), 2,458 postmenopausal women with BMD T-scores of less than -2.0 and a history of at least one vertebral fracture were randomly assigned to receive risedronate 2.5 mg, risedronate 5 mg daily, or placebo.^{56–58} The risk of new vertebral fractures with risedronate 5 mg/day was 41% lower than with placebo at three years ($P = 0.003$), and the risk of new nonvertebral fractures was 40% lower than with placebo ($P = 0.02$). A significant reduction in vertebral fracture risk at the end of the first year was observed with 5 mg.

Risedronate also demonstrated efficacy in preventing hip fractures in the randomized Hip Intervention Program (HIP) trial.⁵⁹ HIP included these groups:

- 5,445 postmenopausal women aged 70–79 with femoral neck BMD T-scores of less than -4.0 or T-scores of less than -3.0 plus one other risk factor
- 3,886 women 80 years of age and older with at least one nonskeletal risk factor or low T-scores (below -4.0 or below -3.0 or less and a hip-axis length of at least 111.1 cm or greater).

Participants received risedronate 2.5 mg or 5 mg/day or placebo. Treatment was associated with a 40% decrease in risk of hip fracture ($P = 0.009$) but did not have a significant impact on hip fracture rates in the 70- to 79-year-old patients. However, only 16% of this older cohort had been recruited on the basis of low BMD; the rest of the subjects had been recruited on the basis of other risk factors, such as a recent fall-related injury.

Ibandronate (Boniva)

The efficacy of ibandronate was shown in the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE), a randomized, placebo-controlled, double-blind study.⁶⁰ Participants were 2,946 postmenopausal women with lumbar spine BMD T-scores of less than -2.0 and at least one but no more than four prior vertebral fractures.

Patients were randomly assigned to receive ibandronate 2.5 mg daily (the “daily” group), ibandronate 20 mg every other day for 12 doses every three months (the “intermittent” group), or placebo. At three years, the risk of new vertebral fracture with

ibandronate, relative to placebo, was reduced by 62% in the daily group ($P = 0.0001$) and by 50% in the intermittent group ($P = 0.006$). The risk reduction for new vertebral fractures was significant after two years.

Etidronate (Didronel)

Etidronate disodium is available in the U.S. in an oral formulation for the treatment of Paget’s disease. In a large, placebo-controlled, double-blind study, 423 generally healthy postmenopausal women were randomly assigned to receive placebo only, phosphate plus placebo, phosphate plus etidronate, or etidronate plus placebo for three years.^{61,62} Phosphate was administered at 1 g twice daily, and etidronate was given at 400 mg daily for 14 consecutive days of a 91-day cycle.

At the end of three years, reductions in fracture risk did not differ between the etidronate and non-etidronate groups. Although the study was not specifically powered to detect a difference in the risk of fracture, there was a 44% reduction in vertebral fractures with etidronate ($P < 0.05$), compared with the non-etidronate groups, for patients with BMD below the 50th percentile (-2.67 or less). ADEs reported in clinical trials with etidronate included leg cramps, headache, gastritis, and arthralgia.⁴⁷

Zoledronic Acid (Reclast, Zometa)

An injectable bisphosphonate, zoledronic acid is approved in the U.S. for use in Paget’s disease, hypercalcemia of malignancy, and bone metastases of solid tumors. Its efficacy in PMO was studied in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial. This was a large double-blind, placebo-controlled study of 3,889 postmenopausal women 65 to 89 years of age.⁶³

Subjects were eligible for enrollment if they had T-scores of -2.5 or less, with or without evidence of an existing vertebral fracture, or T-scores of -1.5 or less, with evidence of two mild vertebral fractures or one moderate vertebral fracture. They were randomly assigned to receive IV zoledronic acid 5 mg or placebo over 15 minutes one time a year for three doses.

Over three years of follow-up and compared with placebo, zoledronic acid therapy reduced vertebral fracture risk by 70% ($P < 0.001$), hip fracture risk by 41% ($P = 0.002$), and non-vertebral fracture risk by 25% ($P < 0.001$). Notable ADEs occurred with zoledronic acid more frequently than with placebo, including an increased incidence of serious atrial fibrillation and elevated serum creatinine levels (above 0.5 mg/dL), but mean creatine clearance did not differ with placebo.

Selective Estrogen Receptor Modulators

Raloxifene (Evista)

Raloxifene (Evista, Eli Lilly) decreases bone resorption through activation and modulation of the estrogenic pathways, thus mitigating bone loss associated with reduction of estrogen levels after menopause. Raloxifene is available in an oral formulation for daily administration.⁶⁴

The efficacy and safety of raloxifene were established in the three-year Multiple Outcomes of Raloxifene Evaluation (MORE) study.^{65,66} MORE was a randomized, blinded, placebo-controlled trial that included 7,705 postmenopausal women with T-scores of less than -2.5 or a low T-score plus a history of fracture. Participants received raloxifene 60 mg/day, 120 mg/day, or placebo.

Postmenopausal Osteoporosis: Treatment Options

At three years, raloxifene 60 mg, the approved dose in the U.S., was associated with a 30% reduced risk of vertebral fractures in women with a pre-existing fracture ($P < 0.05$). The risk reduction in women without a previous vertebral fracture was 50% ($P < 0.05$) and was significant at 12 months. There was no difference in the risk of nonvertebral fractures between raloxifene and placebo. ADEs include leg cramps and hot flashes.⁶⁴

Continuing Outcomes Relevant to Evista (CORE) was a four-year follow-up study of 3,200 patients from the MORE study.⁶⁷ In CORE, patients originally assigned to receive raloxifene 60 mg/day or 120 mg/day continued with raloxifene 60 mg/day; those receiving placebo continued with placebo for four years. The study measured the rate of new nonvertebral fractures. No difference between nonvertebral fracture rates was observed with raloxifene (22.8%) or placebo (22.9%) during the four-year follow-up period. Differences in fracture rates were not significant according to fracture location or in terms of other bone-active agents during the follow-up study. However, women with a prevalent vertebral fracture at the start of MORE had a 22% lower fracture rate with raloxifene compared with placebo ($P < 0.05$). Fracture rates were also 37% lower in women with a severe vertebral fracture at the start of MORE ($P < 0.05$).

Calcitonin

Calcitonin-Salmon (Miacalcin, Fortical)

Calcitonin-salmon (Miacalcin, Novartis; Fortical, Upsher Smith) is a synthetic polypeptide of 32 amino acids found in salmon calcitonin. It is available in the U.S. in an intranasal form for daily use and in subcutaneous form for every-other-day use.^{68,69}

Calcitonin decreases bone resorption by reducing the activity and the number of osteoclasts. The antiresorptive activity of calcitonin is marked initially, but both antiresorptive and bone formation responses decrease over time.⁶⁸ There is evidence *in vitro* that calcitonin may augment bone formation through increased osteoblast activity.

The efficacy and safety of intranasal calcitonin were established in the Prevent Recurrence of Osteoporotic Fractures (PROOF) trial. This large double-blinded, randomized, placebo-controlled study included 1,255 postmenopausal women who received 100 IU, 200 IU, 400 IU, or placebo daily for five years.⁷⁰ Women receiving 200 IU, the approved dose in the U.S., experienced a 33% reduction in new vertebral fractures at five years ($P = 0.03$). The most commonly reported ADEs included rhinitis and back pain.^{68,69}

Anabolic Agents

Parathyroid Hormone (Teriparatide [Forteo])

Teriparatide (Forteo, Eli Lilly) contains the active 1-34 N-terminal amino-acid component of recombinant human PTH and is available as a subcutaneous injection for daily administration.⁷¹ A bone anabolic agent, teriparatide encourages new bone formation on bone surfaces by stimulating osteoblast activity more than osteoclast activity. This agent appears to increase bone density and improve bone architecture.⁷²

The randomized, placebo-controlled Fracture Prevention Trial enrolled 1,647 postmenopausal women with a history of at least two mild vertebral fractures or one moderate vertebral fracture or BMD T-scores of less than -1.0 plus two or more mod-

erate fractures.⁷³

Participants received teriparatide at 20 mcg daily, 40 mcg daily, or placebo. The women who received 20 mcg (the approved dose in the U.S.) had a 65% lower risk of one or more new vertebral fractures, compared with placebo, after an average follow-up period of 17 to 19 months ($P < 0.05$). The 20-mcg patients also had a 53% lower risk of nonvertebral fractures than women receiving placebo ($P < 0.05$).

In clinical studies, common ADEs associated with teriparatide included leg cramps and dizziness.⁷⁰ Teriparatide was also associated with osteosarcoma in rats, and its labeling has a black-box warning against its use in patients with an increased risk of osteosarcoma.⁷¹ One case of osteosarcoma was reported in 300,000 patients treated with teriparatide worldwide, although an association between teriparatide and osteosarcoma was not established in this patient.⁷⁴ Because of a potential risk of osteosarcoma and a lack of data on the drug's long-term use, teriparatide treatment should be limited to two years.

Products in Development

Strontium Ranelate (Protelos)

Strontium ranelate (Protelos, Servier), a compound consisting of the elemental metal, strontium, and ranelic acid, is approved in Europe and Australia for the treatment of PMO to reduce the risk of vertebral and hip fractures.^{75,76} A unique mechanism of action allows for continued bone formation while decreasing bone resorption.⁷⁷ Two published clinical studies have shown its efficacy in the treatment of PMO.^{75,76}

In the Spinal Osteoporosis Therapeutic Intervention trial (SOTI), a three-year placebo-controlled, double-blinded study of 1,649 postmenopausal women with a history of one or more vertebral fractures and low BMD (below 0.840 g/cm^2), subjects were randomly assigned to receive strontium ranelate 2 g daily or placebo.⁷⁵ Over the three-year trial period, the strontium ranelate group of patients had a 41% lower risk of new vertebral fractures than the placebo group ($P < 0.001$).

The randomized, placebo-controlled Treatment of Peripheral Osteoporosis Study (TROPOS) included postmenopausal women aged 74 years or older with femoral neck T-scores of less than -2.5 or women 70 to 74 years of age but with at least one additional fracture risk factor.⁷⁶ A total of 4,932 subjects received strontium ranelate 2 g daily or placebo for three years. Treatment was associated with a 39% reduction in vertebral fractures ($P < 0.001$) and a 16% reduction in the risk of nonvertebral fractures relative to placebo ($P = 0.04$). There was a 15% reduction in hip fracture risk with treatment, but the trend was not significant. However, the study was not powered to detect a difference in hip fracture.

ADEs in clinical trials included transient nausea and diarrhea as well as dermatitis or eczema and headache.^{75,76} It is not known when approval for strontium ranelate will be sought.

Parathyroid Hormone (Preos)

PTH (1-84) (Preos, NPS Pharmaceuticals) is an anabolic agent under FDA review for the treatment of osteoporosis. Unlike teriparatide, it is a full-length human recombinant PTH. It increases bone density by stimulating bone formation and resorption, resulting in a net gain in bone formation.⁷⁸

Treatment of Osteoporosis with Parathyroid Hormone (TOP)

Postmenopausal Osteoporosis: Treatment Options

was a randomized, double-blind trial designed to study the efficacy of PTH (1-84) in preventing vertebral fractures in these groups of postmenopausal women.⁷⁹

- 45 to 54 years of age, T-scores of -3.0 or less
- 55 years of age or older, T-scores of -2.5 , and one to four prevalent vertebral fractures
- 55 years of age or older, T-scores of -2.5 or less, and no previous vertebral fractures
- 55 years of age or older, T-scores of -2.0 , and one to four prior vertebral fractures

In this study, 2,532 women were randomly assigned to receive PTH (1-84) 100 mcg/day or placebo. The treated women had a lower rate of new or worsened vertebral fractures than those taking placebo. The fracture rate was decreased by 58% ($P \leq 0.05$) with PTH (1-84), compared with placebo, if we assume that those who discontinued the trial early did not experience fractures. If we assume that the fracture rates in the group who discontinued equaled the rates for those who completed the trial, fractures were reduced by 40% with PTH (1-84), compared with placebo ($P = 0.05$). If we assume that those who discontinued the trial had fracture rates equal to those in the placebo group, PTH (1-84) reduced fractures by 38% ($P > 0.05$).

In clinical trials, ADEs reported with PTH (1-84) therapy at rates higher than placebo included injection-site reactions, transient hypercalcemia, hypercalciuria, and nausea.⁷⁹ The FDA has issued an approvable letter for PTH (1-84), but approval has been delayed; the FDA is requesting more information about the incidence of hypercalcemia and the delivery device.⁸⁰

PHARMACOECONOMIC CONSIDERATIONS

A review of the literature indicates that published data on the pharmacoeconomics of PMO therapy in the U.S. are limited and inconclusive. Most pharmacoeconomic analyses were conducted retrospectively or were cost-model studies, and most analyses focused on alendronate. Pharmacoeconomic studies are summarized in Table 4.

Only one prospective pharmacoeconomic evaluation was identified in the area of PMO treatment. Derived from the Fracture Intervention Trial (FIT),⁸¹ this analysis identified fracture-related use of emergency departments, hospitals, nursing homes, or rehabilitation hospital services but did not identify drugs in women 55 to 81 years of age with low BMD (T-scores below 0). Chrischilles et al. estimated the cost of fracture-related health care utilization based on Medicare reimbursement rates and other public program fee schedules. In this study, alendronate was associated with significantly lower fracture-related costs, compared with placebo. The estimated cost-benefit was \$181 per treated patient over three years ($P = 0.036$). Total fracture-related costs were also reduced with alendronate by \$190 per treated patient, compared with placebo, although the reduction did not reach significance ($P = 0.114$).

Schousboe et al. published results from three modeling studies by using fracture outcomes data from FIT.⁸²⁻⁸⁴

Model 1

The first study modeled direct medical costs based on Medicare reimbursement rates, drug treatment costs, and in-

direct societal costs related to productivity losses associated with PMO fractures. Assumptions related to quality-adjusted life-years (QALY), associated with PMO and fractures, were drawn from the literature.⁸⁴ An economic model based on five years of treatment was developed to predict the incremental cost-effectiveness ratio (ICER) associated with alendronate therapy, compared with no treatment, by age and T-scores. Specifically, the study estimated the cost to gain one fully productive year of life (one QALY) with alendronate versus not treating a patient with alendronate. The willingness to pay for such a gain depends on the stakeholder; however, the models discussed in this section used \$50,000 per QALY as the cost-effectiveness threshold.

Using a Markov cost-utility model, the investigators estimated the cost for QALY gained for treating women aged 55 to 75 years of age with T-scores in the osteopenia range (-1.5 to -2.4) without a prior history of fracture. ICERs ranged from \$70,732 in a 65-year-old with a T-score of -2.5 to \$382,250 in an 80-year-old woman with a T-score of -1.5 . Thus, using alendronate as prophylaxis in osteopenic women without a history of fracture was not cost-effective.

Models 2 and 3

Two additional alendronate models estimated the cost-effectiveness of treating women 60 to 80 years of age and with T-scores of -1.5 to -2.4 with alendronate after screening for vertebral deformities, or vertebral compromise.^{82,83} The screening techniques consisted of vertebral fracture assessment (VFA) using dual-energy densitometry and traditional x-rays.

One study, which evaluated cost-effectiveness of treatment after VFA, assessed drug costs and direct medical costs, including VFA screening, based on Medicare and other public fee schedules, over five years.⁸² These cost estimates were used to model the cost for a QALY gain associated with alendronate therapy compared with no treatment by age, T-score, and prevalence of vertebral deformities.

A Markov model was used to estimate the cost per QALY gained for treating a woman with a T-score of -1.5 and no existing vertebral deformities with alendronate (compared with no treatment). The study suggested that fracture prevention with alendronate was not cost-effective; the cost per QALY exceeded \$250,000 regardless of age. However, the cost per QALY gained for treating a woman with a T-score approaching -2.5 and with evidence of spinal deformities, as identified by VFA, ranged from \$18,864 for a 60-year-old woman to \$35,631 for an 80-year-old woman. Thus, treating postmenopausal women was cost-effective if T-scores indicated osteoporosis and if there was a previous vertebral deformity.

The third model, which included x-ray screening, calculated the incremental cost per QALY gained with five years of alendronate treatment versus no treatment.⁸³ In this model, treatment with alendronate was not cost-effective, compared with no treatment, in women with T-scores of -1.5 ; the cost per QALY exceeded \$250,000. However, alendronate therapy was cost-effective in women with T-scores from -1.5 to -2.5 and a vertebral deformity. ICERs ranged from \$4,073 for women 70 years of age with T-scores of -2.4 to \$36,457 for women 80 years of age with T-scores of -1.5 .

Treating all women with T-scores of -2.5 with alendronate was cost-effective whether or not they had vertebral deformities. The

Postmenopausal Osteoporosis: Treatment Options

Table 4 Summary of Pharmacoeconomic Studies for Postmenopausal Osteoporosis (PMO) Therapies

Study / Population	Cost and Source	Drug Cost (AWP)	Result
ALEN vs. no treatment ⁸¹ Age: 55 to 81 years; T-score, < 0	Fracture-related medical care over 3 years Public fee schedules	Not included	\$181 savings per treated patient
ALEN vs. no treatment ⁸⁴ Age: 55-75 years; T-score, -1.5 to -2.4 No prior fracture	Fracture-related medical care/Medicare Reduced productivity/literature	\$894/year	\$70,732/QALY (age 65, T-score of -2.5) \$382,250/QALY (age 80, T-score of -1.5)
ALEN vs. no treatment ⁸² Age: 60 to 80 years; T-score, -1.5 to -2.4	Fracture-related medical care, incl. VFA screening/Medicare	\$842/year	>\$250,000/QALY (any age, no vert. deform.) \$35,631/QALY (age 80, T-score ≤ -2.5 + vert. deform.) \$18,864/QALY (age 60, T-score ≤ -2.5 + vert. deform.)
ALEN vs. no treatment ⁸³ Age: 60 to 80 years; T-score, -1.5 to -2.4	Fracture-related medical care (x-ray screening/Medicare, reduced productivity/literature)	\$842/year	>\$250,000/QALY (T-score -1.5) \$30,420/QALY (age 70, with or without vert. deform.) \$42,192 (age 80, no vert. deform.)
ALEN / RISD vs. no treatment ⁸⁵ Age: 65 years; T-score, ≤ -2	Fracture-related medical care/literature	ALEN: \$843/year RISD: \$763/year	ALEN: \$30,000/QALY, approx. \$36,000 per averted hip fracture RISD: \$16,158/QALY, \$17,649 per avoided hip fracture
ALEN versus RAL ⁸⁶ Age: 55 years; new treatment	Fracture, breast cancer, and CHD-related medical care/literature	Not provided	ALEN: \$2,850 per PMO event averted RAL: \$4,180 per PMO event averted, or \$600 per CHD or PMO event avoided
ALEN, TPD, or TPD + ALEN ⁸⁸ PMO women; T-score, -2.5 Prior vertebral fracture	Fracture-related medical care/Medicare	ALEN: \$894/year TPD: 6,720/year	ALEN: \$11,600/QALY TPD: \$172,300/QALY TPD + ALEN: \$156,500/QALY ≤ \$50,000/QALY (age ≤ 70+, T-score of -4.0)

ALEN = alendronate; AWP = average wholesale price; CHD = coronary heart disease; QALY = quality-adjusted life-year; RAL = raloxifene; RISD = risedronate; TPD = teriparatide; TPD + ALEN = teriparatide, followed by alendronate; vert. deform. = vertebral deformity, VFA = vertebral fracture assessment.
Data from Chrischilles EA, et al.,⁸¹ Schousboe JT, et al.,⁸²⁻⁸⁴ Grima D, et al.,⁸⁵ Mullins CD, et al.,⁸⁶ and Liu H, et al.⁸⁸

model estimated costs per QALY gained from \$30,420 for a woman 70 years of age regardless of vertebral deformity to \$42,192 for an 80-year-old and no prior vertebral deformity. Thus, alendronate seems to be cost-effective in treating PMO in women with T-scores above -2.5 with evidence of vertebral deformity and in those women with T-scores approaching the osteoporosis range with or without vertebral deformities.

Two additional studies describe the cost benefit of alendronate compared with other antiresorptive agents.^{85,86}

Grima et al. compared the cost per QALY gained and per hip fracture averted over three years for alendronate and risedronate in women 65 years of age with T-scores of -2.5 or below.⁸⁵ Using a Markov model, the study authors found that risedronate costs were lower and treatment outcomes were better than with alendronate. Compared with no treatment, the model estimated that the cost per QALY gained with risedronate was \$16,158, and the cost of an averted hip fracture was \$17,649. Compared with no treatment, the estimated cost per QALY gained of alendronate exceeded \$30,000, and the estimated cost of averting a hip fracture was \$36,000.

Mullins and Ohsfeldt estimated the cost of preventing one

event in women 55 years of age who started alendronate or raloxifene therapy, compared with no treatment, over the first seven years of treatment.⁸⁶ They evaluated the budgetary impact of osteoporosis treatment, taking into account persistence with medication. Outcome events were defined as a fracture, breast cancer, or myocardial infarction.

Barrett-Connor et al., in a more recent trial, however, found that raloxifene did not demonstrate a reduction in coronary heart disease (CHD), thereby bringing into question the models' assumptions about CHD risk reduction.⁸⁷ When CHD risk reduction was not considered, the cost per event avoided was \$600 for raloxifene and \$2,850 for alendronate. When CHD and breast cancer risk reductions were removed from the model, isolating the effects of treatment on fracture risk reduction, the cost per event avoided with raloxifene was \$4,180. Thus, the cost benefit of raloxifene, compared with alendronate, was primarily a result of the reduction in events unrelated to PMO.

The pharmacoeconomic data on teriparatide are limited; only one published study was identified. Liu et al. evaluated the cost of gaining one QALY with alendronate alone for five years, teriparatide alone for two years, and teriparatide for two years,

Postmenopausal Osteoporosis: Treatment Options

followed by five years of alendronate in women with PMO and T-scores of -2.5 and a prior vertebral fracture.⁸⁸ This microsimulation model found that alendronate alone cost \$11,600 per QALY, compared with calcium and/or vitamin D supplementation. The cost per QALY was \$172,300 for teriparatide alone and \$156,500 for teriparatide followed by alendronate.

The cost-effectiveness of alendronate alone and of teriparatide, followed by alendronate, improved with increasing age and lower BMD T-scores. The cost-effectiveness of sequential therapy was below \$100,000 per QALY for women 50 years of age and older with T-scores of -4.0 and for women 60 years of age and older and T-scores of -3.5 .

ICERs were at or below \$50,000 for women 70 years of age and older with T-scores of -4.0 . Thus, the use of teriparatide was cost effective with alendronate in very-high-risk women.

DISCUSSION

Efficacy

Drugs that treat osteoporosis have proved effective in preventing fractures in women with PMO. Antiresorptive drugs reduced rates of vertebral fractures by 30% to 70%, and teriparatide reduced these rates by 65% to 69%.^{50-53,56,57,60-63,65,66,70,73} Efficacy of treatment in preventing fractures was seen relatively early, typically within 12 to 18 months. However, several extension trials suggest that the preventive effect plateaus over time, with no difference in fracture rates observed between antiresorptive treatment and placebo arms after four to six years of therapy.^{54,55,67} In addition, efficacy was most pronounced in women at greater risk (lower baseline T-scores, older age, fracture history).^{52,61,67,70}

Differences in efficacy between the major classes of agents may be related to differences in their mechanisms of action. However, compliance with medication may also account for some of the difference in efficacy between antiresorptives and teriparatide. Cramer and Gold reported that one-year compliance with oral bisphosphonates was generally low (17% to 78%).⁸⁹ Although once-yearly zoledronic acid (Reclast) is not approved for use in PMO, it helps solve the problem of poor compliance with bisphosphonate regimens and might explain the higher fracture efficacy rates seen with zoledronic acid compared with other bisphosphonates. However, the incidence of serious atrial fibrillation observed with zoledronic acid in the HORIZON trial warrants further evaluation.

Although teriparatide possesses greater efficacy in fracture prevention than other approved antiresorptive agents, several problems are related to its use. First, because of the potential risk for osteosarcoma, teriparatide should not be used for more than two years. However, two years of therapy might not be sufficient for the long-term prevention of fractures.⁷¹ Evidence is emerging that there is benefit to augmenting teriparatide therapy with an antiresorptive agent to maintain bone mass and structural gains over time. However, identifying the most effective combination is important to minimize the risk of the antiresorptive agent's blunting the bone anabolic properties of teriparatide by reducing the rate of bone turnover.

Several trials have studied the effects of combining PTH with a bisphosphonate on bone formation.⁹⁰⁻⁹² Findings have suggested that using PTH prior to a bisphosphonate may ensure that the full effects of PTH are realized, although using PTH following a course of alendronate therapy is also beneficial.

There is no evidence of additional benefit in using PTH and a bisphosphonate concomitantly. The combination of an antiresorptive and an anabolic agent remains to be fully addressed in clinical trials, and studies with fracture endpoints are warranted to measure the impact of combination treatment on clinical outcomes.

Economics of Fracture Prevention

Besides efficacy, the economics of preventing fractures in patients with PMO should be a primary consideration in determining which patients to treat and which drug class to use. At a cost of \$763 to \$894 per year, antiresorptive agents are cost-effective, compared with placebo, when they are used to treat osteoporosis as diagnosed by prior fragility fractures or T-scores below -2.5 plus another risk factor, such as advancing age.⁸²⁻⁸⁴

Antiresorptive therapy for preventing fractures in women with T-scores above -2.5 without a prior fracture or another risk factor is not cost-effective. However, many fractures occur in women with T-scores above -2.5 ; thus, the cost-effectiveness of fracture prevention in lower-risk populations should be reevaluated when generic antiresorptive agents become available.⁹³

At an annual cost of approximately \$6,700, limited data suggest that teriparatide is not cost-effective for PMO when used alone.⁸⁹ Teriparatide plus alendronate was cost-effective only in the highest-risk women 70 years of age and older with T-scores below -4.0 . Even at a higher price, teriparatide has a cost-effective place in the treatment of PMO for those at greatest risk for fracture.

Overall, pharmacoeconomic data for PMO agents are incomplete. Data for antiresorptive agents are largely focused on alendronate; only one published study of teriparatide has been identified. Furthermore, the studies generally rely on BMD measures plus other risk factors such as age and prior fracture as the indicators of risk. As recognized by the WHO, however, BMD measures are not always available or feasible. Thus, cost-effectiveness studies in patients with various combinations of non-BMD risk factors would be useful for clinicians and managed care plans in selecting cost-effective care for broad populations or individuals when BMD data are not available.

Promising products under review for use in the U.S. include strontium ranelate and PTH (1-84). Early trials for these agents have shown a reduced risk of fractures. If they are approved for use in the U.S., pharmacoeconomic evaluations will be warranted to help define a cost-effective role in PMO fracture prevention.

CONCLUSION

Pharmacotherapy is a cost-effective approach to preventing fractures in women with PMO. Antiresorptive drugs are a mainstay of treatment; they are cost-effective in preventing fractures in PMO populations at risk for fractures because of their history of prior fractures, low T-scores, and advancing age.

Teriparatide, the only available bone anabolic agent, has greater efficacy in fracture prevention than the approved antiresorptive agents. Because of the cost of treatment, however, it appears to be cost-effective only when it is combined with an antiresorptive drug and when its use is reserved for very-high-risk populations with multiple risk factors, including advancing age and very low T-scores.

Postmenopausal Osteoporosis: Treatment Options

Both PTH (1-84) and strontium ranelate, which is available outside the U.S., have demonstrated efficacy in preventing fractures in postmenopausal women. Thus, these agents have the potential to enhance therapeutic options. Future pharmacoeconomic studies for these new agents are warranted to identify their cost-effectiveness.

REFERENCES

1. Consensus development conference: Diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 1993;94:646.
2. World Health Organization. *Prevention and Management of Osteoporosis*. Geneva: WHO; 2003.
3. Melton LJ 3rd. How many women have osteoporosis now? *J Bone Miner Res* 1995;10(2):175-177.
4. Ray NF, Chan JK, Thamer M, Melton LJ. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: Report from the National Osteoporosis Foundation. *J Bone Miner Res* 1997;12(1):24-35.
5. Shen T, Howe LH, Lumpkin JR. Osteoporosis in Illinois: Analysis of hospital discharge records from 1992 to 1995. Springfield, IL: Illinois Department of Public Health; 1997. Available at: www.idph.state.il.us/about/epi/pdf/epi97-9.pdf. Accessed October 2005.
6. Burge RT, King AB, Balda A, Worley D. Methodology for estimating current and future burden of osteoporosis in state populations. *Value Health* 2003;6(5):574-583.
7. Kanis J. Diagnosis of osteoporosis and assessment of risk fracture. *Lancet* 2002;359:1929-1936.
8. Bensen R, Adachi JD, Papaioannou A, et al. Evaluation of easily measured risk factors in the prediction of osteoporotic fractures. *BMC Musculoskelet Disord* 2005;5:47.
9. Black DM, Steinbuch M, Palermo L, et al. An assessment tool for predicting fracture risk in postmenopausal women. *Osteoporos Int* 2001;12(7):519-528.
10. Broe K, Hannan M, Kiely D, et al. Predicting fractures using bone mineral density: A prospective study of long-term care residents. *Osteoporos Int* 2000;11:765-771.
11. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women: Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995;332(12):767-773.
12. Dargent-Molina P, Douchin MN, Cormier C, et al. Use of clinical risk factors in elderly women with low bone mineral density to identify women at higher risk of hip fracture: The EPIDOS prospective study. *Osteoporos Int* 2002;13(7):593-599.
13. Dargent-Molina P, Piaux S, Breart G. A triage strategy based on clinical risk factors for selecting elderly women for treatment or bone densitometry: The EPIDOS prospective study. *Osteoporos Int* 2005;16(8):898-906.
14. Fox KM, Cummings SR, Williams E, Stone K. Femoral neck and intertrochanteric fractures have different risk factors: A prospective study. *Osteoporos Int* 2000;11(12):1018-1023.
15. Fujiwara S, Kasagi F, Yamada M, Kodama K. Risk factors for fracture in a Japanese cohort. *J Bone Miner Res* 1997;12(7):998-1004.
16. Gunnes M, Mellstrom D, Johnell O. How well can a previous fracture indicate a new fracture? A questionnaire study of 29,802 postmenopausal women. *Acta Orthop Scand* 1998;69(5):508-512.
17. Ismail AA, Cockerill W, Cooper C, et al. Prevalent vertebral deformity predicts incident hip though not distal forearm fracture: Results from the European Prospective Osteoporosis Study. *Osteoporos Int* 2001;12(2):85-90.
18. Johnell O, Kanis JA, Oden A, et al. Fracture risk following an osteoporotic fracture. *Osteoporos Int* 2004;15(3):175-179.
19. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;312:1254-1259.
20. Johnell O, Kanis J, Oden A, et al. Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 2005;20(7):1185-1194.
21. Kroger H, Huopio J, Honkanen R, et al. Prediction of fracture risk using axial bone mineral density in a perimenopausal population: A prospective study. *J Bone Miner Res* 1995;10(2):302-306.
22. Torgerson DJ, Campbell MK, Thomas RE, Reid DM. Prediction of perimenopausal fractures by bone mineral density and other risk factors. *J Bone Miner Res* 1996;11(2):293-297.
23. Klotzbuecher C, Ross P, Landsman P, et al. Patients with prior fracture have an increased risk of future fractures: A summary of the literature and statistical significance. *J Bone Miner Res* 2000;15(4):721-739.
24. Siris E, Brenneman S, Miller P, et al. Predictive value of low BMD for 1-year fracture outcomes is similar for postmenopausal women ages 50-64 and 65 and older: Results from the National Osteoporosis Risk Assessment (NORA). *J Bone Miner Res* 2004;19(8):1215-1220.
25. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res* 2004;19(6):893-899.
26. De Vries F, Bracke M, Leufkens HG, et al. Fracture risk with intermittent high-dose oral glucocorticoid therapy. *Arthritis Rheum* 2007;56(1):208-214.
27. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. *Osteoporos Int* 2005;16(6):581-589.
28. van Staa TP, Geusens P, Bijlsma JW, et al. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54(10):3104-3112.
29. Kanis J, Johansson H, Johnell O, et al. Alcohol intake as a risk factor for fracture. *Osteoporos Int* 2005;16:737-742.
30. Kanis J, Johnell O, Oden A, et al. Smoking and fracture risk: A meta-analysis. *Osteoporos Int* 2005;16:155-162.
31. Silverman SL. Selecting patients for osteoporosis therapy. *Curr Osteoporos Rep* 2006;4(3):91-95.
32. Brown J, Josse R. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *Can Med Assoc J* 2002;167(10 Suppl):S1-S34.
33. Hodgson SF, Watts NB, Bilezikian JP, et al. American Association of Clinical Endocrinologists: Medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis (2001 ed., selected updates for 2003). *Endocr Pract* 2003;9(6):544-564.
34. Heinemann D. An overview of the National Osteoporosis Foundation clinical practice guidelines. *Geriatrics* 2000;55(5):31-39.
35. National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. November 8, 2005. Available at: www.nof.org/physguide/attention_phys.htm.
36. Rodan G, Fleisch H. Bisphosphonates: Mechanisms of action. *J Clin Invest* 1996;97(12):2692-2696.
37. Fleisch H. Bisphosphonates: Mechanisms of action. *Endocr Rev* 1998;19(1):80-100.
38. Fosamax (alendronate sodium), prescribing information. Whitehouse Station, NJ: Merck; February 2006.
39. Actonel (risedronate sodium), prescribing information. Bridgewater, NJ: Procter & Gamble; August 2006.
40. Boniva (ibandronate), prescribing information. Nutley, NJ: Roche; August 2006.
41. Boniva Injection (ibandronate), prescribing information. Nutley, NJ: Roche; January 2006.
42. Rizzoli R, Greenspan SL, Bone G 3rd, et al. Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. *J Bone Miner Res* 2002;17(11):1988-1996.
43. Schnitzer T, Bone HG, Crepaldi G, et al. Alendronate Once-Weekly Study Group. Therapeutic equivalence of alendronate 70 mg once weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Aging (Milano)* 2000;12(1):1-12.
44. 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(2):103-111.
45. Delmas P, 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(6):1838-1846.
46. 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(5):654-661.
47. Didronel (etidronate), prescribing information. North Norwich, NJ:

Postmenopausal Osteoporosis: Treatment Options

- Procter & Gamble; May 2005.
48. Zometa (zoledronic acid), prescribing information. East Hanover, NJ: Novartis; December 2005.
 49. Aredia (pamidronate), prescribing information. East Hanover, NJ: Novartis; February 2006.
 50. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med* 1995;333(22):1437-1444.
 51. Black D, Cummings S, Karf D, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fracture. *Lancet* 1996;348:1535-1541.
 52. Cummings S, Black D, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone mineral density but without vertebral fractures: Results from the Fracture Intervention Trial. *JAMA* 1998;280(24):2077-2082.
 53. Black D, Thompson D, Bauer D, et al. Fracture risk reduction with alendronate in women with osteoporosis: The Fracture Intervention Trial. *J Clin Endocrinol Metab* 2000;85(11):4118-4124.
 54. Bone HG, Hosking D, Devogelaer J-P, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004;350(12):1189-1199.
 55. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: The Fracture Intervention Trial Long-term Extension (FLEX): A randomized trial. *JAMA* 2006;296(24):2927-2938.
 56. Roux C, Seeman E, Eastell R, et al. Efficacy of risedronate on clinical vertebral fractures within six months. *Curr Med Res Opin* 2004;20(4):433-439.
 57. Harris T, Watts N, Genant H, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: A randomized controlled trial. *JAMA* 1999;282(4):1344-1352.
 58. Harrington J, Ste-Marie L, Brandi M, et al. Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. *Calcif Tissue Int* 2004;74:129-135.
 59. McClung M, Geusens P, Miller P, et al. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001;344(5):333-340.
 60. Chesnut C, Skag R, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004;19(8):1241-1249.
 61. Watts N, Harris S, Genant H, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990;323(2):73-79.
 62. Harris S, Watts N, Jackson R, et al. Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: Three years of blinded therapy followed by one year of open therapy. *Am J Med* 1993;95(6):557-567.
 63. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356(18):1809-1822.
 64. Evista (raloxifene HCl), prescribing information. Indianapolis, IN: Eli Lilly & Co.; 2003.
 65. Ettinger B, Black DM, Mitlak BH, et al. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: Results from a 3-year randomized clinical trial. *JAMA* 1999;282(7):637-645.
 66. Maricic M, Adachi J, Sarkar S, et al. Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis. *Arch Intern Med* 2002;162:1140-1143.
 67. Siris ES, Harris ST, Eastell R, et al. Skeletal effects of raloxifene after 8 years: Results from the Continuing Outcomes Relevant to Evista (CORE) Study. *J Bone Miner Res* 2005;20(9):1514-1524.
 68. Miacalcin (calcitonin-salmon), prescribing information. East Hanover, NJ: Novartis; June 2006.
 69. Fortical (calcitonin-salmon), prescribing information. Minneapolis, MN: Upsher Smith; June 2006.
 70. Chesnut C, 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). *Am J Med* 2000;109:267-276.
 71. Forteo (teriparatide), prescribing information. Indianapolis, IN: Eli Lilly & Co.; 2004.
 72. Dempster D, Cosman F, Kurland E, et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: A paired biopsy study. *J Bone Miner Res* 2001;16(10):1846-1853.
 73. Neer R, Arnaud C, Zanchetta J, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;334(19):1434-1441.
 74. Harper KD, Kregel JH, Marcus R, Mitlak BH. Osteosarcoma and teriparatide? *J Bone Miner Res* 2007;22(2):334.
 75. Meunier P, 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.
 76. Reginster J, Seeman E, De Vernejoul M, 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.
 77. Reginster J, Sarlet N, Lejeune E, Leonori L. Strontium ranelate: A new treatment for postmenopausal osteoporosis with a dual mode of action. *Curr Osteoporos Rep* 2005;3(1):30-34.
 78. Hodsmann A, Hanley D, Ettinger M, et al. Efficacy and safety of human parathyroid hormone (1-84) in increasing bone mineral density in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2003;88(11):5212-5220.
 79. Greenspan SL, Bone HG, Ettinger MP, et al. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: A randomized trial. *Ann Intern Med* 2007;146(5):326-339.
 80. NPS receives approvable letter for Preos NDA. Salt Lake City, UT: NPS Pharmaceuticals. Available at: www.nps.com/news/relasetxt.php?ReqId=830043. Accessed March 10, 2006.
 81. Chrischilles EA, Dasbach EJ, Rubenstein LM, et al. The effect of alendronate on fracture-related healthcare utilization and costs: The Fracture Intervention Trial. *Osteoporos Int* 2001;12:654-660.
 82. Schousboe JT, Ensrud KE, Nyman JA, et al. Cost-effectiveness of vertebral fracture assessment to detect prevalent vertebral deformity and select postmenopausal women with a femoral neck T-score >-2.5 for alendronate therapy: A modeling study. *J Clin Densitom* 2006;9(2):133-143.
 83. Schousboe JT, Ensrud KE, Nyman JA, et al. Potential cost-effective use of spine radiographs to detect vertebral deformity and select osteopenic postmenopausal women for amino-bisphosphonate therapy. *Osteoporos Int* 2005;16(12):1883-1893.
 84. Schousboe JT, Nyman JA, Kane RL, Ensrud KE. Cost-effectiveness of alendronate therapy for osteopenic postmenopausal women. *Ann Intern Med* 2005;142:734-741.
 85. Grima D, Burge RT, Becker DL, Tosteson ANA. Short-term cost-effectiveness of bisphosphonate therapies for postmenopausal osteoporotic women at high risk of fracture. *P&T* 2002;27(9):448-455.
 86. Mullins CD, Ohsfeldt R. Modeling the annual costs of postmenopausal prevention therapy: Raloxifene, alendronate or estrogen-progestin therapy. *J Manage Care Pharm* 2003;9(2):150-158.
 87. 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(2):125-137.
 88. Liu H, Michaud K, Nayak S, et al. The cost-effectiveness of therapy with teriparatide and alendronate in women with severe osteoporosis. *Arch Intern Med* 2006;166(11):1209-1217.
 89. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int* February 17, 2007 (electronic version).
 90. Cosman F, Nieves J, Zion M, et al. Daily and cyclical parathyroid hormone in women receiving alendronate. *N Engl J Med* 2005;353(6):566-575.
 91. Black D, Greenspan S, Ensrud K, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med* 2003;349(13):1207-1215.
 92. Black D, Bilezikian J, Ensrud K, et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med* 2005;353(6):555-565.
 93. Wainwright SA, Marshall LM, Ensrud KE, et al. Hip fracture in women without osteoporosis. *J Clin Endocrinol Metab* 2005;90(5):2787-2793. ■