Bisphosphonates for the Prevention and Treatment of Osteoporosis

Lisa Anne Boothby, PharmD

INCIDENCE AND PREVALENCE

Osteoporosis currently affects 20 million people in the U.S., and the total number of osteoporosis-related fractures is expected to increase substantially over the next 50 years.1-3 The estimated lifetime risk of hip fracture for white women after age 50 is 16%, with the risk of vertebral fractures exceeding 30%.2-4 In addition, more than 20% of patients who experience a hip fracture die within one year, and another 20% require indefinite long-term care that further expends health care resources and decreases quality of life.1-3

With more than 300,000 hospital admissions per year due to osteoporotic hip fractures among estrogen-deficient women, the result is an excess of $9 billion in direct medical costs.5 As a consequence of the economic burden and decreased quality of life, initiatives to prevent osteoporosis should be among the practitioner’s top priorities. In women who already have osteoporosis, practitioners should recommend nonpharmacological and pharmacological interventions to stabilize bone mineral density and to prevent bone fractures.

RISK ASSESSMENT AND PREVENTION

Postmenopausal osteoporosis is a condition characterized by low bone mass, deterioration of bone tissue leading to bone fragility, and subsequent susceptibility to fractures.5 Clinical practice guidelines for the treatment of osteoporosis that were derived from evidence-based medicine,6 as well as the Consensus Development Panel on Osteoporosis Prevention,7 agree on derived from evidence-based medicine,6 as well as the Consensus Development Panel on Osteoporosis Prevention,7 agree on the need for bone mass assessments and clinical practice guidelines for the treatment of osteoporosis that were derived from evidence-based medicine,6 as well as the Consensus Development Panel on Osteoporosis Prevention,7 agree on the need for bone mass assessments and the need for appropriate treatment.6,7 If dual x-ray absorptiometry (DXA) is used to assess BMD, a T-score of –1 to –2.5 indicates osteopenia whereas a T-score of –2.5 or less suggests osteoporosis.6,7 The assessment of risk factors, in addition to BMD scores, may help to identify those women at highest risk for fractures, to prevent fracture and to begin both nonpharmacological and pharmacological therapies.6,7 Pharmacological therapy is recommended for all postmenopausal women with T-scores below –2.0 or those with T-scores below –1.5 with osteoporotic risk factors. In addition, clinical practice guidelines recommend that all postmenopausal women with vertebral or hip fractures begin osteoporosis treatment.6,7

Examples of nonmodifiable risk factors for osteoporotic fractures include:

- a personal history of fracture in a first-degree relative
- Caucasian race
- age greater than 65 years
- female sex
- low BMD
- poor health

Patients with osteopenia or osteoporosis are at even greater risk when multiple risk factors confound low BMD scores.8,9 Potentially modifiable risk factors include current cigarette smoking,4 alcoholism, and inadequate physical activity.4,7,8 Causes of estrogen deficiency, such as menopause before 45 years of age and premenopausal amenorrhea for more than one year, increase osteoporosis risk as well.6

PREVENTION OF OSTEOPOROSIS

Preventive measures for decreasing the risk of osteoporosis in high-risk patients include the identification and treatment of all secondary causes of osteoporosis, including:9,11,12

- endocrine or metabolic diseases
- nutritional conditions such as malnutrition, alcoholism, and calcium deficiency
- certain drug therapies (e.g., corticosteroids)
- collagen metabolism disorders

In addition, decreasing doses or minimizing the use of certain sedatives and anticholinergics (e.g., amitriptyline and diazepam) that impair coordination may decrease the risk of falling.7 Preventive therapy is recommended for osteopenia, including weight-bearing exercise, nonpharmacological lifestyle changes, adequate calcium and vitamin D intake, and HRT for postmenopausal women without contraindications.7,8

Calcium and Vitamin D

To prevent osteoporosis, adequate calcium intake is essential.10 Patients should maintain an adequate diet consisting of foods containing calcium and vitamin D. If dietary calcium intake is inadequate, patients should take oral calcium and vitamin D supplements. The latest clinical practice guidelines recommend a daily calcium intake of 1200 to 1500 mg/day, depending on age, menopausal status, and concurrent hormone replacement therapy (HRT).6,7 Vitamin D is also essential for calcium absorption and utilization. For patients at risk for osteoporosis, an intake of 200 to 800 International Units (IU) of vitamin D per day is recommended.6,7

The effect of calcium and vitamin D supplementation on bone

Dr. Boothby is Affiliate Clinical Assistant Professor at Harrison School of Pharmacy, Auburn University, in Auburn, Alabama; Drug Information Coordinator at Columbus Regional Drug Information Center, The Medical Center, Department of Pharmacy, in Columbus, Georgia; and Adjunct Clinical Assistant Professor at Southern School of Pharmacy, Mercer University, in Atlanta, Georgia.
density in men and women 65 years of age and older was shown in a three-year, double-blind, randomized, controlled clinical trial. Patients received 500 mg of elemental calcium supplementation in addition to their normal diet and 700 IU of cholecalciferol taken at bedtime. Serum osteocalcin concentrations were 9% lower in the men and 14% lower in the women than at baseline levels. In addition, a significant decrease in nonvertebral fractures was seen (P = .02) after three years. Adequate calcium intake is necessary for all patients, especially those with multiple risk factors for osteoporosis.

**Hormone Replacement Therapy**

HRT is approved for the prevention and treatment of osteoporosis, and the Food and Drug Administration (FDA) has approved both oral and transdermal estrogens for the prevention of bone loss in new-onset menopause. On the basis of its effectiveness in osteoporosis prevention and treatment, as well as in its ability to decrease vasomotor symptoms, HRT may provide the greatest efficacy for the lowest cost. Controversy clouds this issue because of the potential increased risk of breast cancer associated with long-term use and the risk of deep vein thrombosis (DVT) associated with both short-term and long-term use.

Although large, randomized, controlled clinical trials have been conducted to assess the risks and benefits of HRT, more studies are needed to further elucidate all benefits and risks.

The Women’s Health Initiative was a multicenter, randomized, double-blind, placebo-controlled clinical trial conducted in postmenopausal women (n = 16,608). Women receiving continuous, combined HRT in the form of conjugated estrogens (0.625 mg and medroxyprogesterone 2.5 mg) experienced a statistically significant decrease in hip, vertebral, other osteoporotic, and total osteoporotic fractures (hazard ratio [HR] = 0.76 [0.69–0.85]). A combined total endpoint (the global index) was calculated to estimate the benefits and risks of therapy. Because of the lack of overall benefit per global index scores and the incidence of invasive breast cancer reaching the stopping boundary z-score, the estrogen/medroxyprogesterone arm of the study was halted three years early. The authors suggest a five-year timeline when there might be an increased breast cancer risk.

**Calcitonin and Selective Estrogen Receptor Modulators**

Calcitonin is a hormone that inhibits bone resorption. It is available in the form of an FDA-approved nasal spray for the treatment of osteoporosis. Nasal calcitonin is considered a safe and effective intervention for osteoporosis. Calcitonin has an added analgesic benefit for osteoporotic and metastatic bone pain. It can be used alone or in combination with HRT or bisphosphonates.

A randomized, double-blind, placebo-controlled trial was conducted to assess the efficacy of calcitonin nasal spray to reduce the risk of new vertebral fractures. A 33% relative risk reduction (RRR) in new vertebral fractures was obtained with nasal calcitonin (200 units/day) (RR = 0.67 [0.47 to 0.97]; P = .03). However, results for groups given 100 IU and 400 IU were not statistically significantly different from those receiving placebo.

Therefore, these efficacy data should be further corroborated in prospective clinical trials because of the lack of dose response. This is especially true because calcitonin nasal spray is an expensive drug therapy.

Raloxifene (Evista®, Eli Lilly) has been approved by the FDA for the prevention of osteoporosis. It belongs to a class of agents called selective estrogen receptor modulators (SERMs). Raloxifene is indicated for osteoporosis prevention, but data on the prevention of hip fractures are limited. The drug has been used in combination with bisphosphonates and calcitonin (see “Combination Therapy”). Raloxifene has been shown to decrease the risk of vertebral fractures within one year of treatment (P < .001) and has been associated with a significant decrease in breast cancer risk after three years of treatment (P < .001).

### Table 1 FDA-Approved Indications and Uses for Bisphosphonates in the U.S. 31–35

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Indication and Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>5 mg PO q.d.; 10 mg PO q.d. 35 mg q wk; 70 mg PO q wk 40 mg PO q.d.</td>
<td>Postmenopausal osteoporosis prevention and treatment Paget’s disease</td>
</tr>
<tr>
<td>Etidronate</td>
<td>400 mg PO q.d.</td>
<td>Paget’s disease</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>30 mg IV q.d.; 4-hr infusion x 3 days 60 mg IV infusion over 4 hr x 1 dose 90 mg IV infusion over 2 hr every 3–4 wk 30 mg IV infusion over 2 hr every 3 mo</td>
<td>Paget’s disease Hypercalcemia of malignancy Osteolytic bone lesions Postmenopausal osteoporosis treatment Prevent glucocorticoid-induced osteoporosis</td>
</tr>
<tr>
<td>Risedronate</td>
<td>5 mg PO q.d. 35 mg PO q wk 30 mg PO q.d. x 3 mo</td>
<td>Postmenopausal osteoporosis prevention and treatment Prevent glucocorticoid-induced osteoporosis Paget’s disease</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>4 mg IV infusion over 5 min once per year</td>
<td>Postmenopausal osteoporosis treatment Hypercalcemia of malignancy</td>
</tr>
</tbody>
</table>

* Non-FDA-approved uses.

FDA = Food and Drug Administration; IV = intravenous; PO = by mouth; q = every; q.d. = each day.
Bisphosphonates

Bisphosphonates are considered an alternative therapeutic modality for women who meet BMD criteria for treatment but cannot tolerate HRT, for women who have not succeeded with HRT treatment, or for women who are at an increased risk of breast or endometrial cancer. Bisphosphonates are also a cost-effective option for both the prevention and treatment of osteoporosis.

Alendronate (Fosamax®, Merck) was the first bisphosphonate approved by the FDA for the prevention and treatment of osteoporosis. It reduces the incidence of fracture (spine, hip, and wrist) by approximately 50% (P < .001) in patients with osteoporosis and increases BMD by 4.4% (P < .001). Other available oral and intravenous (IV) bisphosphonates include etidronate, pamidronate, risedronate, and zoledronic acid (Table 1).

Pharmacology and Pharmacokinetics

Bisphosphonates act directly to inhibit normal and abnormal bone resorption. The mechanism of action may involve dissolution of hydroxyapatite crystals or inhibition of osteoclast mediated bone resorption. Bisphosphonates undergo little to no metabolism. The drug adsorbs to areas of bone osteogenesis and is slowly eliminated with a plasma half-life approaching 72 hours. Excess quantities of the drug are eliminated unchanged in the urine and feces. Bisphosphonates are incorporated into bone in a nonpharmacologically active form, which has a terminal half-life approaching 10 years. When the drug is released from bone, it is again capable of inhibiting osteoclastic activity. Food significantly decreases systemic absorption of all oral bisphosphonate dosage forms.

Indications for Bisphosphonates

FDA-approved indications for bisphosphonates include the prevention and treatment of osteoporosis and management of Paget’s disease of the bone, a chronic disorder that results in excessive bone breakdown and formation, causing fractures, skeletal abnormalities, and significant bone pain. Other FDA-approved indications include heterotrophic ossification, hypercalcemia of malignancy, breast cancer, and multiple myeloma.

Intravenous bisphosphonates are not currently FDA-approved for the treatment of postmenopausal osteoporosis. Unlabeled uses include hyperparathyroidism and reduction of bone pain associated with prostatic cancer. Dose, frequency, and indications for specific bisphosphonates are listed in Table 1.

Clinical Trials

Numerous meta-analyses of randomized, controlled clinical trials have confirmed the efficacy and safety of bisphosphonates for the prevention and treatment of osteoporosis and for the prevention of glucocorticoid-induced osteoporosis (Table 2). In addition, many randomized, controlled clinical trials have been conducted to examine the effects of bisphosphonates on BMD, risk of fracture, and gastrointestinal adverse events (Table 3).

Two randomized, double-blind, placebo-controlled clinical trials were conducted over a three-year period to evaluate the long-term safety and efficacy of alendronate. After completion of the first three years of the original studies, 727 women consented to continue participating in a double-blind, two-year extension. The placebo group was switched to alendronate 10 mg/day in a blinded fashion. After completion, a second two-year extension was conducted, maintaining the double-blind treatment assignments. Women who received 20 mg initially, then 5 mg in years three to five, received placebo for the last two years (totaling seven years). BMD was assessed and compared at month 60 against baseline BMD with an intent-to-treat analysis. There were no significant changes in BMD at the spine or the hip, but significant declines in BMD occurred at the total body lumbar spine and femoral neck.

Table 2 Meta-analysis of Bisphosphonates for FDA-Approved Indications

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Patient Status</th>
<th>Drug Therapy</th>
<th>Primary Endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macedo et al38</td>
<td>1,587</td>
<td>Postmenopausal osteoporosis treatment</td>
<td>ERT vs. placebo; calcitonin vs. placebo; bisphosphonates vs. placebo</td>
<td>Effect size</td>
<td>Bisphosphonates provided greater increases in BMD versus calcitonin or ERT (P &lt; .001)</td>
</tr>
<tr>
<td>Cranney et al39</td>
<td>1,010</td>
<td>Postmenopausal osteoporosis treatment and prevention</td>
<td>Etidronate vs. placebo</td>
<td>Risk of vertebral and nonvertebral fractures</td>
<td>Etidronate decreased vertebral fractures and increased BMD in lumbar spine and femoral neck (RR = 0.6% [0.41–0.88])</td>
</tr>
<tr>
<td>Homik et al40</td>
<td>842</td>
<td>Steroid-induced osteoporosis</td>
<td>Any bisphosphonates used in clinical trials for steroid-induced osteoporosis</td>
<td>BMD in lumbar spine and femoral neck; risk of spinal fracture Non-vertebral fracture risk</td>
<td>Bisphosphonates increased BMD in lumbar spine (4.3% [2.7–5.9]) and femoral neck (2.1% [0.01–3.8]); no difference in spinal fracture risk detected</td>
</tr>
<tr>
<td>Karpf et al42</td>
<td>1,677</td>
<td>Postmenopausal osteoporosis treatment</td>
<td>Alendronate vs. placebo</td>
<td>Any GI adverse event</td>
<td>Alendronate decreased RR of nonvertebral fracture by 29% (P = .048)</td>
</tr>
<tr>
<td>Taggart et al43</td>
<td>10,068</td>
<td>Postmenopausal osteoporosis treatment and prevention</td>
<td>Risedronate 5 mg/day for 3 years vs. placebo</td>
<td></td>
<td>Risedronate GI ADRs were not SS different versus placebo (P = .77)</td>
</tr>
</tbody>
</table>

ADR = adverse drug reaction; BMD = bone mineral density; ERT = estrogen replacement therapy; FDA = Food and Drug Administration; GI = gastrointestinal; RR = relative risk; SS = statistically significant.
Bisphosphonates for the Prevention and Treatment of Osteoporosis
and forearm (P < .05). These data support the safe and effective use of bisphosphonates (e.g., alendronate) over the long term. Although there was a statistically significant decrease in BMD in total body and forearm, the bone turnover remained below baseline levels, suggesting the possibility of “drug holidays” without bisphosphonates for periods of time. The optimal intervals for treatment or drug holidays have yet to be confirmed.49

In the Fracture Intervention Trial, 2,027 women with osteoporosis and a history of one or more morphometric vertebral fractures at baseline were randomly assigned to receive alendronate 5 mg/day for two years, then alendronate 10 mg/day thereafter for 4.3 years total or placebo for 4.3 years. The relative risk reduction of 42% (RR = .58 [90.41–0.81]) in multiple symptomatic fractures was seen in the alendronate group compared with those taking placebo.52 Therefore, assuming that patients are treated for five years with alendronate 10 mg/day, the number needed to treat to prevent one fracture is 21. In contrast, according to the Woman’s Health Initiative, published in 2002,16 the number needed to treat for HRT to prevent one osteoporotic fracture was more than twice as many, at 47. A similar result was seen in another recent clinical trial conducted by the Vertebral Efficacy with Risedronate Therapy (VERT) Study Group.56 The investigators compared the efficacy of risedronate 2.5 mg/day versus placebo for three years’ duration. The risedronate 2.5-mg arm was discontinued after one year. Risedronate 5 mg/day was associated with a 41% decrease with risedronate 5 mg/day versus placebo for three years’ duration. Risedronate 5 mg/day was associated with a 41% decrease in new vertebral fractures over three years (18% to 58%), and the number needed to treat to prevent one fracture was 20.

Combination Therapy

Because of a lack of evidence-based medicine to support the use of two antiresorptive agents when the clinical practice guidelines were written, the use of combination pharmacological therapy has not yet been recommended. However, mounting evidence supports the efficacy of combination therapy to further increase BMD and to decrease fractures (see Table 3).8,44–58

A phase III randomized, double-blind study was conducted to compare the efficacy of raloxifene 60 mg plus alendronate 10 mg with alendronate 10 mg with placebo on BMD. The greatest changes in BMD were seen in the raloxifene and alendronate group (P < .02).45

Another clinical trial was undertaken to assess the efficacy of estradiol 2 mg plus alendronate 10 mg versus estradiol 2 mg plus alendronate 5 mg on BMD in patients with surgically induced menopause. No statistically significant differences were noted between the groups, but both groups showed increased BMD compared with baseline levels.46

The role of combination therapy will remain controversial until more evidence is available to guide treatment decisions. In the meantime, weight-bearing exercise is encouraged for most patients to help maintain BMD, usually in addition to drug therapy and calcium supplementation.6

### Extending the Bisphosphonate Dosing Interval

The trend toward increasing the bisphosphonate dosing interval continues. Initially, the standard of care consisted of daily oral bisphosphonate dosing for the prevention and treatment of osteoporosis. The pharmacokinetic and pharmacodynamic properties of bisphosphonates, however, suggest that an extended dosing interval may be appropriate because the dosing interval for most maintenance medications typically spans two or three plasma half-lives. This is of interest because extending the dosing interval may increase patient compliance without resulting in a change in adverse effects.53

The clinical trials that were conducted examined the relative incidence of adverse effects when bisphosphonates were dosed

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Designation</th>
<th>Drug Therapy</th>
<th>Follow-up</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donahue et al, 2002</td>
<td>50,000</td>
<td>Ret. Cohort</td>
<td>Alendronate vs. matched cohort without alendronate</td>
<td>Two years’ retrospective claims data</td>
<td>No difference detected (power = 65% post hoc)</td>
</tr>
<tr>
<td>Lanza et al, 2000</td>
<td>515</td>
<td>R, SB, PA, M</td>
<td>Risedronate 5 mg vs. alendronate 10 mg</td>
<td>Endoscopy in 2 weeks and at baseline</td>
<td>Gastric ulcer incidence: rise in ulcer development with alendronate</td>
</tr>
<tr>
<td>Marshall et al, 2000</td>
<td>76</td>
<td>R, SB, PA, PC</td>
<td>ASA 650 mg vs. alendronate 10 mg vs. placebo</td>
<td>Endoscopy in 2 weeks and at baseline, and PGE2 serum concentrations</td>
<td>Gastric ulcers: 24/26 in ASA group, 17/25 in alendronate group, 13/25 in placebo group</td>
</tr>
<tr>
<td>Lanza et al, 2002</td>
<td>277</td>
<td>R, DB, PC, AC, PA</td>
<td>Alendronate 70 mg weekly a 10 wk vs. placebo x 10 wk vs. ASA 650 mg qid x 1 wk</td>
<td>Endoscopy within 5–7 days of last drug dose and at baseline</td>
<td>No difference between 70 mg and placebo in gastric erosion scores (P = .745)</td>
</tr>
<tr>
<td>Taggart et al, 2002</td>
<td>10,000</td>
<td>MA</td>
<td>Risedronate vs. placebo</td>
<td>Endoscopy and subjective patient reports of ADE</td>
<td>No difference versus placebo</td>
</tr>
</tbody>
</table>

AC = active control; ADE = adverse drug event; ASA = aspirin; M = multicenter; MA = meta-analysis; PC = placebo-controlled; PGE2 = prostaglandin E2; R = randomized; SB = single-blind; SS = statistically significant; PA = parallel; Ret = retrospective.
daily and weekly, and a difference in adverse effects was not detected. For osteoporosis treatment, risedronate and oral alendronate are commercially available in once-weekly dosage forms. Although not approved by the FDA for the treatment of osteoporosis, IV pamidronate has been administered once every 3 months and IV zoledronic acid has been administered once per year for this indication. Increased compliance in this case may be more theoretical than actual. Extending dosing intervals with other drug therapies, as well as utilizing unique extended-release dosage forms for chronic disease states such as hypertension, has been shown to increase compliance.

Adverse Drug Reactions

The most commonly reported adverse events associated with the oral bisphosphonates in clinical trials were chest pain, abdominal pain, dyspepsia, and nausea (Table 4). Hypocalcemia, hypophosphatemia, and hypomagnesemia were most often associated with IV pamidronate and were dose-dependent. Adverse effects associated with the 70-mg alendronate weekly dosage form were similar to those of the 10-mg once-daily regimen, with abdominal pain and dyspepsia being the main gastrointestinal adverse effects. Patients should be monitored for abdominal pain, and alendronate should be discontinued if pain occurs. Risedronate was associated with headache and diarrhea in clinical trials. Arthralgias and a flu-like syndrome were reported with the use of both risedronate and pamidronate. These effects may be transient and do not necessarily warrant discontinuation.

Contraindications to Oral Bisphosphonates

Contraindications to bisphosphonate therapy include allergy, hypocalcemia, esophageal abnormalities, and the inability to remain upright for 30 minutes after taking a dose. Patients with renal insufficiency should not take alendronate if the creatinine clearance is less than 35 ml/minute. Patients should not take risedronate if the creatinine clearance is less than 30 ml/minute. Patients should not take etidronate if the serum creatinine is greater than 5 mg/dl.

Patient Counseling

Appropriate patient counseling is the key to decreasing GI adverse effects, improving compliance, and ensuring optimal outcomes. Patients should be counseled to take alendronate on awakening in the morning with a full glass of water, before eating, drinking other beverages, or taking any other medications. Patients should wait at least 30 minutes before eating food or drinking beverages other than water. Patients must avoid lying down for 30 minutes after taking the medication to prevent esophageal irritation. Because of the increased risk of upper GI adverse effects and the potentially decreased bioavailability of alendronate, aspirin should not be taken concomitantly with alendronate. Risedronate has been shown to be effective when administered at least 30 minutes before the first meal or drink of the day, even though the greater bioavailability occurs when risedronate is administered in a fasting state 10 hours after and four hours prior to food consumption. Like alendronate, risedronate should be swallowed with a full glass of water while the patient is in an upright position. Patients should not lie down for 30 minutes after taking oral bisphosphonates.

Antacids and calcium-containing supplements should not be taken at the same time as oral bisphosphonates, although they can be taken at least two hours apart. Calcium carbonate in doses of 1,200 to 1,500 mg/day should be taken in three divided daily doses with meals to increase absorption. Patients should wait at least one hour after taking oral bisphosphonates before taking other medications.

Formulary and Cost Implications

In comparisons of annual costs of oral and IV formulations, once-weekly risedronate and once-yearly zoledronic acid are the least expensive bisphosphonates (Table 5). Once-weekly alendronate or risedronate might promote increased compliance and a decreased need for spacing other medications, as well as food, apart from the morning bisphosphonate dose. This situation is especially problematic in hospitalized patients, who are typically lying in bed receiving multiple drug therapies. In addition to the twice-weekly and once-weekly oral dosage forms, it is possible that once-daily risedronate and alendronate might remain on many hospital formularies. Alendronate is included on most ambulatory care formularies, such as advanced Patient Care Services (PCS) and the Veterans Administration (VA) formulary, with 62% of the current market share. As a consequence of the increasing incidence of osteoporosis, risedronate is projected to increase its market share over the next 10 years. By the year 2008, the drug is projected to become a billion-dollar product.

Market Share

Bisphosphonates are emerging as the preferred regimen for both preventing and treating osteoporosis, among other indications. In 2001, the IMS Health Survey of the U.S.-selected osteoporosis market, ending November 2001, reported that bisphosphonates held 35.3% of the market share. Estrogens and estrogens/progestins combined held 32.8% and 16.5% of the market share, respectively, with SERMs following at 10% and calcitonin last, at 5.3%. With the continued incidence of osteo-
Bisphosphonates for the Prevention and Treatment of Osteoporosis

porosis expected to increase, the demand for bisphosphonates is expected to rise substantially.

FUTURE DRUG THERAPIES

Two new bisphosphonates, icandronate and ibandronate, are in clinical trials. It is not clear whether these new agents will offer any advantage over the currently available bisphosphonates. Other drug therapy options that require more evidence-based medicine include parathyroid hormone, strontium renelate, and peroxisome proliferator-activated receptor (PPAR) gamma modulators. Low-dose medroxyprogesterone acetate (Prempro®, Wyeth-Ayerst) is also expected to gain FDA approval because the recent Women’s Heart Outcomes Prevention Evaluation (HOPE) study demonstrated similar BMD effects with much lower estrogen doses and fewer adverse effects. Efforts to promote disease prevention based on predisposing factors should remain a top priority as we recommend pharmacological and nonpharmacological modalities.

As the controversies surrounding HRT continue to baffle the medical profession, bisphosphonates may become the preferred therapeutic modality for osteoporosis prevention and treatment. Future research initiatives should include large-scale experimental studies to assess long-term outcomes of combination-therapy regimens, optimal dosing intervals, and genetic predisposing factors that may lead to increased fracture risk.

REFERENCES

Bisphosphonates for the Prevention and Treatment of Osteoporosis


