

REPORT

Treating & Preventing Osteoporosis
Sizing up bisphosphonates

Page 1 of 2

FDA-approved estrogen-progestin drugs increase the risk of heart attack, stroke and breast cancer. The evidence has become so overwhelming that the National Institutes of Health just halted one of the largest clinical studies because too many women taking estrogen-progestin drugs were developing lethal diseases. The startling results of this latest study appear in the July 17, 2002 issue of the *Journal of the American Medical Association (JAMA)*. According to the *New York Times* (July 9, 2002), these findings are a "shock to the medical system" because so many doctors have prescribed these hormone drugs to women.

Members of The Life Extension Foundation, on the other hand, learned long ago about the lethal dangers of estrogen drugs and synthetic progestins. The Foundation recommended low-cost alternatives such as DHEA replacement, natural progesterone cream and plant-based phytoestrogens. When estrogen replacement was absolutely necessary, The Foundation recommended safer forms such as "estriol" that is widely used in Europe.

One reason women expose themselves to risks of estrogen drugs is to protect their bones against osteoporosis. The osteoporosis epidemic is one of the most serious health problems confronting aging women, as it can cause chronic pain, disability and premature death. The good news is that there are safe approaches to protect the skeleton. In this article, we discuss in meticulous detail the proven benefits of bisphosphonate drugs in reversing the loss of bone density.



By Angela Pirisi

Most commonly a risk for those over the age of 50, the Osteoporosis Society of Canada reports that one in four women and one in eight men in that age group suffers from the disease. Meanwhile, the National Osteoporosis Foundation calls osteoporosis "a major health threat" to almost 44 million U.S. women and men, aged 50 and older, or just over half of the population in this age group. Being female and postmenopausal (due to estrogen deficiency), and having a slight build are leading risk factors, while lifestyle factors include calcium and vitamin D deficiency, physical inactivity, as well as alcohol, caffeine and tobacco consumption. Other risk factors include fewer births, light eyes, hair and skin, and a family history of the disease. Osteoporosis can also stem from long-term use of certain medications, such as corticosteroids, or disease complications, as in the case of cancer, Crohn's and liver disease. However, some people, particularly men, develop the disease without any known cause or risk factors-what's known as idiopathic osteoporosis.

Combating the disease

Fortunately, medical science has been chipping away at solutions to prevent, slow and reverse the destructive effects of osteoporosis. Currently, a number of therapies are used-often in some combination-such as estrogen replacement therapy, calcitonin, calcium plus vitamin D supplementation and fluoride salts. Another class of agents used to treat osteoporosis are bisphosphonates, which are essentially bone-rebuilding drugs. These include: alendronate (Fosamax), tiludronate (Skelid), pamidronate (Aredia), etidronate (Didronel), risedronate (Actonel), and zoledronic acid (Zometa). Bisphosphonates work primarily by decreasing resorption (bone breakdown). The net result is an increase in bone mineral density (BMD) and a reduced risk of fractures.[1-2] German researchers, who reviewed a number of studies, concluded that, "From systematic research the best external evidence is available for a supplementation with calcium and vitamin D and a therapy with the bisphosphonates alendronate or risedronate, as well as the selective estrogen receptor modulator raloxifene (Evista)."[3]

To date, many studies have shown that bisphosphonates are effective for treating osteoporosis and preventing it in high-risk groups, particularly postmenopausal women. At the University of Heidelberg, Germany, bisphosphonates have been shown to prevent

vertebral fractures in osteoporotic patients, and reduce the incidence of new fractures of the femoral neck in those with pre-existing fractures. The authors write that, "The introduction of bisphosphonates into the treatment of osteoporosis is definitely an enrichment of the therapeutic spectrum in conjunction with the basic treatment comprising calcium, vitamin D, diet and physical measures." [4]

The two bisphosphonates, etidronate and alendronate, for example, have been proven to increase bone mass and decrease fracture incidence by 50%, compared to control rates at the spine, hip and other sites in postmenopausal women. [5] Meanwhile, researchers in New Zealand reported similar results following a two-year randomized, double blind, placebo-controlled study of pamidronate (150 milligrams per day) in 48 postmenopausal women with osteoporosis. Findings showed that the bone mineral density, which was measured at six-month intervals, revealed a progressive increase in the entire body, at all skeletal sites, while no significant changes occurred in the placebo group. There were nearly twice as many fractures per year occurring in the placebo group (24 per 100) than in the pamidronate group (13 per 100). [6] Also, a South American study found that 100 milligrams daily of oral pamidronate in postmenopausal women with confirmed osteoporosis resulted in a low rate of height loss, and significantly lower incidence of total number of new fractures and new hip fractures. [7]

BISPHOSPHONATE DRUGS		
NAME	GENERIC NAME	DOSAGE
FOSAMAX*	ALENDRONATE	10 MG/DAY or 70 MG/WEEK
ACTONEL*	RISEDRONATE	5 MG/DAY
ARELIA	PAMIDRONATE (i.v. injection)	30-90 MG/MONTH
ZOMETA	ZOLEDRONIC ACID (i.v. injection)	4 MG/YEAR
SKELID	TILUDRONATE	400 MG/DAY
DIDRONEL	ETIDRONATE	5 MG/DAY

The bisphosphonate drugs listed above have a narrow range of safety and must be prescribed by a knowledgeable physician.

*Actonel and Fosamax are the only bisphosphonate drugs that are presently approved in the U.S. for the treatment of osteoporosis.

In larger experiments, such as the Vertebral Efficacy with Risedronate Therapy (VERT) study, investigators looked at 2,458 women under 85 with postmenopausal osteoporosis and at least one vertebral fracture. Subjects were randomly assigned to oral risedronate 2.5 or 5 milligrams per day or placebo for three years. All received 1,000 milligrams calcium per day, and those with low vitamin D levels received up to 500 international units (IU) per day. The three-year, 5 milligrams treatment decreased the cumulative incidence of new vertebral fractures by 41% and invertebral fractures by 39%. Bone mineral density increased significantly, compared with placebo, at the lumbar spine (5.4% versus 1.1%), femoral neck (1.6% versus -1.2%) and at other measured sites. [8]

The most definitive data regarding postmenopausal women comes from the U.S.-based Fracture Intervention Trial (FIT), the largest osteoporosis clinical trial to date involving over 6,000 women aged 54 to 81. Researchers examined the effect of daily alendronate in 2,027 women with vertebral compression fractures over a three-year period, and in 4,432 without fractures over a four-year period. In the group with existing fractures, they found that alendronate increased bone mineral density by 8% at the spine and 5% at the hip, while decreasing the incidence of all clinical fractures from 18.2% in placebo to 13.6% in the treated group, and vertebral compressions decreased from 15% to 8%. [9] However, differences were not significant between the test and placebo group in the study arm looking at women without baseline fractures. [10] All participants reporting calcium intakes of 1,000 milligrams per day or less received a supplement containing 500 milligrams of calcium and 250 international units (IU) of vitamin D. Subjects were randomly assigned to either placebo or 5 milligrams per day of alendronate sodium for two years, changing to 10 milligrams per day for the remainder of the trial. Results showed that alendronate increased bone mineral density at all sites studied and reduced clinical fractures from 312 in the placebo group to 272 in the intervention group, although not significantly (14%).



Studies have also demonstrated that bisphosphonates are effective for osteoporosis resulting from secondary or unknown causes. For example, in cancer patients, bisphosphonates are standard treatment for hypercalcemia of malignancy (HCM), a skeletal complication that affects more than 10% of all cancer patients, and 20% to 40% of advanced cancer cases. It is especially common in patients with bone metastases, and those with breast and prostate cancer account for about 80% of bone metastases. Overstimulated osteoclasts result in an increased rate of bone resorption, causing bone weakening, while excess calcium makes its way into the bloodstream and creates complications, such as dehydration, fatigue, nausea,

vomiting, confusion and coma.[11]

In a Belgian study, researchers gave 26 patients with either age-related or glucocorticoid-induced osteoporosis 60 milligrams of pamidronate intravenously every three months for one year. Researchers found that after only three months of treatment, patients' pain score, due to chronic back pain from osteoporotic vertebral fractures, fell from 3.2 to 1.2 in both osteoporotic groups.[12] Meanwhile, Australian researchers suggest that, based on medical literature, postmenopausal women receiving corticosteroids should be given bisphosphonates, vitamin D metabolite or hormone replacement (in that order) to prevent or reverse associated bone loss.[13]



In Denmark, researchers examined the effect of 10 milligrams daily of alendronate on lumbar spine bone mineral density in 32 patients with low bone mineral density, due to Crohn's complications, for 12 months. Bone density increased by 4.6% in the lumbar spine and 3.3% in the hip in the alendronate group, respectively, compared to a decrease of 0.9% and 0.7% at the same sites in the placebo group. Authors concluded that 10 milligrams daily of alendronate increased bone mineral density in patients with Crohn's disease and was safe and well tolerated.[14]

Likewise, in liver disease and liver transplant patients, for whom osteoporosis is a common complication, giving intravenous bisphosphonates (pamidronate) preoperatively prevented fractures in high-risk patients. Patients were treated with pamidronate every three months, before surgery and for nine months afterwards, and compared to an untreated group. None of those receiving bisphosphonate therapy (0 out of 13) suffered postoperative fracture, whereas 31% of those who went untreated did.[15]

Continued on Page 2 of 2

[click here for more information on Bone Assure](#)

[Back to the Magazine Forum](#)

REPORT

Page 2 of 2

Possible mechanisms

Researchers know that bisphosphonates have an incredible affinity for bone, binding to calcium and building up in the mineralized bone matrix, so that it's more resistant to breakdown by osteoclasts. Still, it's not perfectly clear how they work. It is suspected that bisphosphonates affect signaling between osteoblasts and osteoclasts. Some in vitro studies have suggested that bisphosphonates may initiate macrophage death, thereby also overcoming their deleterious effects on osteoblasts. Macrophages are found on osteoblasts, and are thought to have some responsibility for excessive bone resorption, namely by impeding the activity and survival of osteoblasts. Researchers found that adding bisphosphonates to co-cultures of osteoblasts and macrophages blocked the adverse effects of macrophages on osteoblasts. Bisphosphonates increased the number of osteoblasts by 82%, and reduced the number of macrophages. Also, control co-cultures revealed fewer osteoblasts than the treated ones.[16]

Because of various modes of action observed in studies, bisphosphonates have been classified into two groups. Bisphosphonates that closely resemble pyrophosphate—a normal by-product of human metabolism (such as clodronate and etidronate) are incorporated into adenosine triphosphate (ATP) analogues, which create compounds that are believed to build up and lead to osteoclast death.[17] The newest generation of bisphosphonates, which contain nitrogen (such as pamidronate, alendronate, risedronate and ibandronate), are believed to inhibit protein prenylation (post-translational modification) within the mevalonate pathway. The mevalonate pathway is responsible for the biosynthesis of cholesterol, other sterols and isoprenoid lipids. Isoprenoid lipids are key in the prenylation of intracellular signaling proteins (GTPases) that, when activated, regulate a number of processes, including osteoclast activity. It's believed that by impeding the function of these regulatory proteins, bisphosphonates result in blocking osteoclast functioning and causing apoptosis.[4]

Weighing pros & cons

Besides attempting to unravel how bisphosphonates work, researchers are also aiming to address their benefits and risks. The fact that bisphosphonates bind so strongly to bone and confine their activity to the skeleton has made clinicians confident about their safety profile. The positive aspect of bisphosphonates is that, because their effects are limited to bones, adverse effects elsewhere in other body tissues and organs are minimal.[2] However, thanks to their antiresorptive properties, bisphosphonates have been accused of substantially reducing bone turnover, in turn, impairing microdamage repair and causing increased bone mineralization, which can increase bone fragility. Thus, it's important to weigh how, "Osteoporosis therapies may also affect bone architecture by causing the redistribution of bone structure. Restructuring of bone during treatment may change bone fragility, even in the absence of drug effects on bone mineral density (BMD)."[18]

Bisphosphonates also have some side effects, regardless of their narrow target of action. The most commonly reported side effects of oral bisphosphonates are gastrointestinal complications, such as esophagitis, gastritis and diarrhea.[19] Intravenous delivery of bisphosphonates is being examined as a way to sidestep gastrointestinal adverse effects for those who cannot tolerate oral bisphosphonates, as well as a strategy to reduce dosing frequency significantly. There are adverse effects related to intravenous administration too, such as iritis (inflammatory eye disorder), muscle aches and fever.[1]

Knowing more

Studies are attempting to elucidate how bisphosphonates work best, the question focusing on delivery modes (oral versus intravenous) and dosing amount and frequency. While some research has looked at intermittent dosing, given every few weeks or months, the latest findings reported in the New England Journal of Medicine suggest that just one annual injection of the bisphosphonate, Zometa (zoledronic acid), boosts bone mineral density as well as more frequently dosed oral bisphosphonates.[20] In the study led by a New Zealand team of scientists, 351 postmenopausal women with low bone mineral density were randomized into five different treatment regimen groups: 0.25 milligrams, 0.5 milligrams, or 1 milligram given every three months; a 2-milligram dose every six months; or a single 4-milligram dose; or an inactive placebo. Increases in bone mineral density were reported among all Zometa-treated patients, which were comparable to increases associated with a daily regimen of any of the three oral bisphosphonates: Actonel, Fosamax and Aredia. Larger studies with a 5



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milligram dose of Zometa are underway, one involving over 8,000 men and postmenopausal women with osteoporosis, while another includes about 3,000 men and postmenopausal women.

Another question being investigated is whether bisphosphonates are preferable to other treatments for the purpose of preventive therapy in high-risk groups. Some studies have debated whether bisphosphonate therapy is appropriate for patients under 60 with osteopenia (low bone density) without fractures. Generally, bisphosphonates have been indicated for individuals with established osteoporosis or at high risk of the disease. A large UK study called the Early Postmenopausal Intervention Cohort Study Group weighed bisphosphonates against hormone replacement therapy (HRT). Investigators looked at the effect of 2.5 versus 5 milligrams of alendronate per day or placebo on bone mineral density in 1,174 postmenopausal women under the age of 60. Also, 435 more women were randomized to receive alendronate, a placebo or combination estrogen-progestin therapy. Results showed that controls lost bone mineral density at all measured sites. Contrarily, women receiving 5 milligrams of alendronate daily had an average increase in bone mineral density of 3.5% at the lumbar spine, 1.9% at the hip and 0.7% for the total body. Women treated with 2.5 milligrams of alendronate daily had smaller increases in bone mineral density. And the estrogen-progestin combination showed a 1% to 2% better response rate than a 5-milligram dose of alendronate.[21] While the study's authors concluded that bisphosphonates were comparable to hormone replacement therapy, others argue that HRT is still the best mode of preventive therapy in postmenopausal women because of additional beneficial effects on other organ systems, and not just bones.[22]

Finally, researchers are still delving further into the question of how appropriate bisphosphonates are for treating osteoporosis in men, as the majority of studies have focused on women. It remains to be seen whether they work as well in men as they do in women, although clinical experience would suggest that's the case. Also, some research now demonstrates that bisphosphonates positively affect bone mineral density in men with idiopathic or secondary osteoporosis.[23-24] Preliminary data from a large, placebo-controlled trial of alendronate in men with osteoporosis also suggests a positive effect on bone mineral density.[25]

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[Back to the Magazine Forum](#)

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