New drugs hold promise for osteoporosis

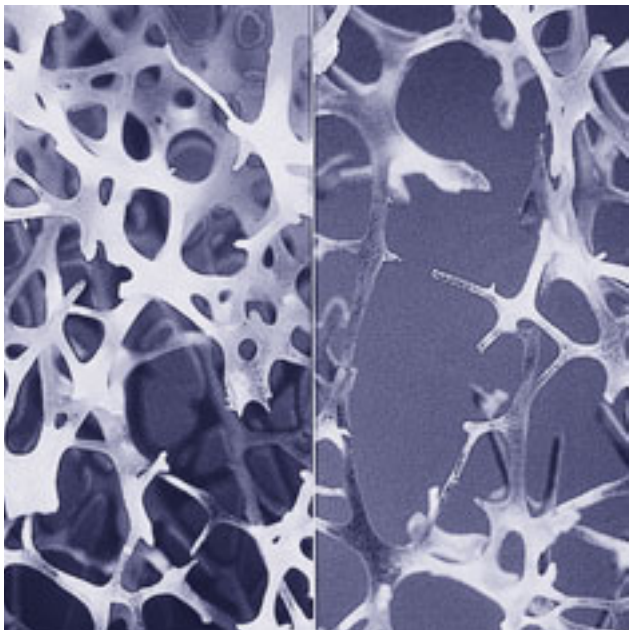
Although a potentially debilitating disease, with treatment it can be prevented.

BY LINDA RICHARDS

Felicia Cosman, physician and director of the National Osteoporosis Foundation, believes orthopedic surgeons miss many cases of osteoporosis. "People who have specific fractures go to orthopedic surgeons, and they generally fix the fracture; however, that patient may also have an underlying bone weakness—that's the link that's not getting made," says Cosman, whose organization is working with the American Orthopaedic Association to increase awareness. "If you have an atraumatic fracture as an adult—most importantly an event with a spine or hip fracture—you have osteoporosis and require treatment."

Also, many practitioners and patients view bone fragility from osteoporosis-related deterioration as an inevitable outcome of aging. But to Cosman, osteoporosis causes bad aging. "Not being able to walk much, or requiring a walker, or not breathing well because of back fractures—these take away huge quality of life," she points out. "We want people to age well; we don't have to have fractures as our consequence."

Osteoporosis treatment has other challenges besides underdiagnosis. Even when it's diagnosed, many practitioners are reluctant to start what may be lifetime therapy with many current medications. Or they are confused by a fuzzy correlation between fracture reduction and a drug's improvement in bone mass density (BMD), the current gold standard of bone mass. Not helping the picture are the results of the 2002 Women's Health Initiative on hormone-replacement therapy, a menopausal treatment many women had been using for its bone-saving benefits. The study that showed estrogen unequivocally reduced fracture risk also showed increased breast cancer risk with long-term estrogen and progestin use.



INTERNATIONAL OSTEOPOROSIS FOUNDATION

Figure 1. Osteoporotic bone (right) shows structural deterioration relative to healthy bone.

Fosamax still leading

Researchers deal with two sides of a skeletal equation when developing treatments for osteoporosis. First, the bone mass attained through a person's mid-20s is an important determinant of lifelong skeletal health. At the same time, in a process called bone turnover or remodeling, old bone tissue is replaced with new bone. Around age 50, bone loss begins to outpace bone growth, increasing at a rate of about 0.5% every year. Men are born with stronger, thicker bones to begin with, while women experience accelerated bone loss that jumps during the five years around menopause. Rates then stabilize, but research shows men and women in their 80s undergo another acceleration in bone loss, says Jane Cauley, associate professor of epidemiology at the University of Pittsburgh and osteoporosis epidemiology researcher.

Genetics plays a role in both parts of the equation, with about 70% of bone mass under genetic control. As for other risk factors, Cosman says their priority is being reordered, with more importance assigned to risks such as fracture history, age, weight, and BMD measurement. "Perhaps the newest concept is bone turnover measurement—most view [an above normal] bone turnover rate as a risk factor."

Until two years ago, all osteoporosis drug therapies worked on the bone-loss part of the skeletal equation: They slow breakdown, allowing bone replacement to exceed bone loss. Alendronate, Merck's bisphosphonate called Fosamax, is the leading drug for treating and preventing postmenopausal osteoporosis. Launched in 1995, Merck's Fosamax sales hit $2.7 billion in 2003, up 19% from the previous year. "Alendronate is extremely effective at improving fracture risk, shown in both patients with prior fractures and with prevention of fractures," Cosman says.

Despite a significantly later launch, Procter & Gamble's (P&G's) bisphosphonate, Actonel, has nabbed one-third of new bisphosphonate prescriptions and should hit $1 billion in global sales this year, according to the company. Cliff Rosen, an osteoporosis specialist and researcher at St. Joseph Hospital in Bangor, ME, attributes P&G's success to aggressive marketing: "The drugs are the same—there's no difference in gastrointestinal side effects."

In 1997, raloxifene became the first in a class of drugs called serotonin estrogen receptor modulators (SERMs) to be

approved for osteoporosis treatment in postmenopausal women. Sold as Evista by Eli Lilly, the first-generation SERMs work like estrogen, but apparently without the risk of breast and uterine cancer, although some women experience hot flashes. Novartis's nasal spray, Miacalcin, which contains the parathyroid hormone calcitonin, is another popular but slightly less effective medication, and it currently comprises 12% of new nonhormonal osteoporosis prescriptions.

Teriparatide, the parathyroid hormone (PTH) launched as Forteo by Lilly in late 2002, became the first anabolic drug to add bone mass instead of slowing bone breakdown. But it's been a long road for PTH. Claude Arnaud, a professor of medicine at the University of California, San Francisco, had spent years studying how the natural hormone regulated bone metabolism and blood calcium. Given short-term, PTH stimulated bone growth, but given long-term it had the nasty effect of damaging it.

However, Arnaud was convinced that injections over a short time and in a certain way—under the skin rather than directly into a vein—would lead to bone formation. Four years after starting a PTH trial in men with osteoporosis, results confirmed his prediction. "The increases in bone density were so huge in some patients that I let Eli Lilly and other drug companies know that this might represent a cure for osteoporosis," he says.

However, the pioneering drug has its hurdles: Approved only for men and women for whom other osteoporosis therapies have failed, it's a daily injection that carries a $7000 annual price tag. Arnaud believes an oral PTH preparation will eventually become available with exclusive or almost exclusive bone formation activity. Asked how soon, Arnaud says the proof of concept will occur "within the next five years." It will have, he adds, "a high probability of forming the basis of a cure. That cure will not be immediate but will be achievable in two to three years of treatment."

Despite the number of existing major products, osteoporosis remains an untapped market. According to a 2003 report from Theta Reports, the total world market for osteoporosis drugs surpassed an estimated $5 billion in 2002 and is projected to exceed $11.5 billion by 2006. And in its annual results, Merck reports that "fewer than 25% of women with osteoporosis in seven major markets (the United States, Canada, the United Kingdom, France, Italy, Germany, and Spain) have been diagnosed and treated."

A new-generation pipeline

The osteoporosis pipeline boasts six Phase III drugs: three new-generation SERMs that will also target other symptoms, two third-generation bisphosphonates, and another PTH medication.

Farthest along is a recombinant PTH called PREOS by NPS Pharmaceuticals, which expects to file for approval by year-end for a potential launch in early 2006. Whereas Forteo contains the first 34 amino acids of the 84-amino-acid chain needed to stimulate bone formation, PREOS is the full-length chain. As to whether there's a difference, NPS says it's determining the significance of the subtle differences between the two drugs.

Hoffman-La Roche received U.S. approval for a daily oral bisphosphonate in 2003, but the company is waiting for a once-monthly version of ibandronate filed in May. Not a bad move, Cosman says, since the oral doses carry restrictive instructions.

The other third-generation bisphosphonate is a yearly intravenous drug, zoledronic acid, developed by Novartis. According to John Orloff, the company's vice president of clinical development and medical affairs, like its potent predecessors Fosamax and Actonel, half of the nitrogen-containing bisphosphonate goes directly to the bone, where it should have a half-life similar to Fosamax's 12 years. "With zoledronic acid, we deliver the entire annual dose in an intravenous form that allows convenient dosing for patients and physicians," he explains. "We know adherence to therapy is not good in osteoporosis, and this form guarantees compliance." The product's first label will be a

Osteoporosis at a glance

Definition	Characterized by low bone mass and structural deterioration of bone tissue
Prevalence	10 million people in the United States (80% women, 20% men)
Effects	50% of women and 25% of men over age 50 will have an osteoporosis-related fracture. The disease is responsible for more than 1.5 million fractures annually.
Cost	Estimated $17 billion spent in 2001 on osteoporotic and related fractures
Symptoms	Often none
Risk factors	Fractures after age 50; low bone mass; thin or small body frame; gender; age; family history; use of some medications; estrogen, vitamin, or calcium deficiency
Detection	Bone density or bone loss testing
Prevention	Diet, exercise, no smoking or excessive alcohol intake

Source: National Osteoporosis Foundation.

single intravenous dose for Paget's disease, now going through the regulatory review process in Europe.

The new-generation SERMs are another group to watch for both osteoporosis and menopausal treatment, as they work to minimize the current SERM side effects of hot flashes and venous thrombosis. "If we can improve women's bone density in their 50s so they have fewer adverse events later in life, these designer drugs will be an excellent choice in the prevention of osteoporosis," Rosen says.

Wyeth's SERM is bazedoxifene, a tissue-selective estrogen receptor–modulator that prevents estrogen from being stimulated in the breast and uterus. Bazedoxifene has a positive bone profile and is neutral in terms of hot flashes and menopausal symptoms, a Wyeth spokeswoman says. Currently in Phase III, an oral form for preventing and treating osteoporosis will be launched first, followed by a version combined with conjugated estrogen for preventing and treating premenopausal symptoms. If they work, Cosman believes SERMs such as bazedoxifene will provide a compelling treatment for many women scared by the Women's Health Initiative results. "This avoids the need to give progesterone, which is the part of hormone therapy that confers the greatest risk to the heart in the first year and the long-term health of the breast," she says.

Lilly's SERM, arzoxifene, is in various stages of Phase III trials in 20 countries. "Phase II studies showed [better] potency and bioavailability than SERMs on the market," says Sondra McQueary, Lilly's osteoporosis global media relations manager. Then there's Pfizer's SERM, lasofoxifene, targeted for a breast cancer prevention indication as well as osteoporosis. "If we do have a drug that can both prevent breast cancer and prevent fractures, it will be very compelling," Cosman says.

Two other medication possibilities for osteoporosis include strontium ranelate, a bone-seeking compound being researched primarily in Europe that has shown vertebral and nonvertebral fracture reduction, and the statins, which continue to show fracture reduction. Rosen, who attended a meeting on anabolics in May, expects to see innovative anabolic drugs that will tap high-risk people before they develop the debilitating disease. "These are designer drugs that target bone-forming cells rather than the bone-dissolving cells. It's all very exciting."

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