By Maryann Napoli

The Marketing of Osteoporosis

How a risk factor became a disease.

Nurses probably get the same question I often get as a consumer advocate. *Should I be on this drug?* You're asked because you're seen as the expert—or, in my case, as simply a knowledgeable friend. More people should ask this question, and they'd be well advised to look beyond the prescriber for answers.

In the name of prevention, millions of Americans have accepted the idea that it's reasonable to treat a risk factor such as bone loss or high cholesterol as if it were a disease. Think back to the 1990s, when virtually all menopausal women were advised—pressured, according to accounts that came my way—by their gynecologists to go on hormone replacement therapy to prevent heart disease and hip fractures. Recall how the pressure let up abruptly in 2002, when the Women's Health Initiative trial of estrogen plus progestin had to be halted three years short of its intended goal because participants taking the hormone combination showed an increased risk of heart disease, stroke, blood clots, and breast cancer.

More people should question the wisdom of starting long-term drug therapy. Often the magnitude of the risk factor has been overestimated, or the danger of the disease itself exaggerated, by people trying to sell you something—like a drug you must take for the rest of your life.

LOW BONE DENSITY: A RISK FACTOR THAT BECAME A DISEASE

The osteoporosis story is an excellent example of how the pharmaceutical industry begins to create a market for a new prevention drug years before it's approved. The disease has become a major health concern for older women,[1] though it was largely unknown to the general public until the early 1980s. That's when the pharmaceutical industry–funded osteoporosis awareness campaign began with coverage on radio and TV and in magazines like *Vogue, McCall's,* and *Reader's Digest*.[2] It used to be that osteoporosis was not diagnosed until a fragility fracture had occurred. But a new definition, one based on bone mineral density, was established in 1993 at a World Health Organization (WHO) meeting of osteoporosis researchers. Its ostensible purpose was to determine the global prevalence of osteoporosis, but this meeting is where the definition of osteoporosis was radically changed. What had been simply a risk factor (bone loss) became a disease (osteoporosis), complete with an arbitrary cutoff (bone density that's 2.5 standard deviations or more below the normal bone mass in *young* women).[2] Overnight, the market for bone drugs had been expanded. Years after that WHO meeting, I learned that several pharmaceutical companies had sponsored it.[2] Hormone drugs were the standard preventive treatment for osteoporosis at the time of the meeting, but three years later the first nonhormonal drug exclusively for bone loss—alendronate (Fosamax)—was launched.

Getting symptom-free women to accept drug therapy requires scary statistics that imply the danger period starts right after menopause—leaving the impression that hip fractures, the most disabling consequence of osteoporosis, occur soon after the hot flashes are over. Here's one statistic you see often: *24% of women, aged 50 and over, die within a year of a hip fracture*.[3] And here's one you don't see often: *virtually all hip fractures occur after the age of 65 and the majority occur after age 75*.[4] Elderly men have hip fractures, too, but the early marketing of alendronate was all about the ladies.

HOW PREDICTIVE ARE BONE SCANS?

In the initial phase of the industry-funded osteoporosis awareness campaign, the scan known as dual-energy X-ray absorptiometry (DXA) was advised for women at the time of menopause. Scanning caught on in a big way, especially after Merck, the maker of alendronate, began financing the installation of DXA

machines in doctors' offices.[5] Nothing creates drug customers faster than getting people to be routinely screened. That's why Merck's ads aimed at women didn't even mention alendronate; they simply said, "Ask your doctor whether a bone density test is right for you." Sure, smoking, low calcium or vitamin D intake, scatter rugs, poor muscle strength, certain long-acting medications, and impaired vision were given lip service as contributing factors to osteoporotic fractures, but loss of bone density has always been front and center.

Women who got their osteoporosis instructions from the celebrity-loving media read quotes like this from actress and singer Rita Moreno: "Bone density tests are the most important thing for a woman who is reaching or into menopause. It's vitally important that she get measured and find out what her bone health is about."[6] Actress and singer Debbie Reynolds wrote a letter to syndicated advice columnist Ann Landers, urging all postmenopausal women, "You must take this test." Both celebrities made frequent forays in the media on behalf of osteoporosis awareness and appeared to have only women's best interests at heart. That both were paid spokespersons for initiatives funded by Merck would not be disclosed until years later.[6] Merck and the nonprofit National Osteoporosis Foundation used these and other celebrities like Meredith Vieira to get younger women tested. (By 2002, Debbie Reynolds had moved on to another industry-funded gig, raising our collective awareness of the rigors of having an overactive bladder, a "disease" entirely created by Pharmacia, the drug company that developed tolterodine [Detrol], which is now made and marketed by Pfizer.[7])

Celebrity advice aside, research did not support the DXA scanning of well women at or near menopause as a means of predicting future fractures. One can have low bone mass at age 48, for example, and not suffer a hip fracture in old age. Conversely, one can have good bone density at age 48 and have a hip fracture at age 79. This paradox was pointed out as early as 1997 in a report from the British Columbia Office of Health Technology Assessment, which—to my knowledge—was also the first source to reveal industry sponsorship of that 1993 WHO meeting where osteoporosis was redefined.[2] This report had no effect on U.S. testing guidelines, but consumer advocate Barbara Mintzes summed up the situation nicely: "Bone mineral density testing is a poor predictor of future fractures but an excellent predictor of start of drug use."[8]

HOW GOOD IS THE DRUG?

In the initial phase of DXA promotion, many women in early middle age with low bone density but no history of fracture were prescribed alendronate, despite the fact that the drug had been tested only in elderly women with vertebral fractures. And the results, even in this supposedly high-risk group, were not impressive. In the Merck-sponsored three-year trial that won the drug Food and Drug Administration (FDA) approval, hip fractures occurred in 1% of those on alendronate, compared with 2% of those on a placebo.[9] (A "50% reduction in hip fracture" is the accurate, though misleading, way these results were often portrayed.)

Here is where the nurse can serve as a sounding board for women trying to decide whether to go on drug therapy, helping them to interpret this data by considering questions like: *Are you similar in age and fracture history to the women in this trial? What does 1% fewer hip fractures mean to you? Let's compare that 1% benefit with the 1.5% risk of an alendronate-induced esophageal ulcer found in this trial? Consider what happened to the study participants who did not take alendronate* (98% of the untreated women—that is, the placebo group—did *not* have a hip fracture). The "script" for this discussion is taken from the drug's official FDA-approved label and the *Physicians' Desk Reference,* where the trials that won the drug FDA approval are described.

In addition, when alendronate was put to the test in elderly women with bone loss but no vertebral fractures, the four-year trial showed that the hip fracture rate was virtually no different for the drug-treated participants than it was for the women taking a placebo (1% vs. 1.4%, respectively).[9]

In short, alendronate was good at improving bone density but not at reducing hip fractures. This did not stop other drug companies from introducing their own alendronate knockoffs—risedronate (Actonel), ibandronate (Boniva), pamidronate (Aredia), and zoledronic acid (Zometa). All are in the drug class called bisphosphonates.

Long-term harms emerging. The bisphosphonates provide an example of how long a drug class has to be on the market before the full picture of harm is known. The FDA reported in 2008 that bisphosphonates carry the risk of severe and sometimes incapacitating musculoskeletal pain.[10] Worse, an unusual type of severe fracture of the femur has shown up recently in case reports.[11-13] Though rare (so far), these atypical low-energy fractures are alarming because of the odd symptom pattern described by many women. Their thigh bones ached inexplicably for months or weeks and then broke spontaneously while they were walking or standing. Virtually all these fractures occurred in people taking alendronate for more than five years. There have been numerous reports of osteonecrosis of the jaw in people taking bisphosphonates, and not just among those taking the drugs intravenously during cancer treatment. In January the *Journal of the American Dental Association* published a study describing an increased risk of

For more information, visit http://courses.washington.edu/bonephys/ophome.html, the Web site of bone physiologist and osteoporosis researcher Susan Ott, MD, associate professor in the Department of Medicine at the University of Washington in Seattle.

osteonecrosis of the jaw from even short-term oral use of alendronate.[14]

How long alendronate and other bisphosphonates should be taken has been a lingering question ever since the drugs went on the market. It's doubtful the many women who received a prescription were told they were participating in a vast experiment to answer that question. Here's how Dr. Susan Love described the problem in 1997: "Bisphosphonates are drugs that act by binding to the osteoclasts (the cells that resorb bone), preventing them from functioning; this decreases bone loss in menopausal women. The fact that these drugs decrease bone loss, however, doesn't mean that they actually build bone. Also, although we know that they decrease fractures in the short term, we don't know what they do in the long term. Because they interfere with the balance between resorption and buildup, they may eventually affect the architecture of the skeleton."[15]

MISLEADING DOCTORS

Why middle-aged rather than elderly women became the likely recipients of an alendronate prescription is no mystery. Merck's initial ads aimed at physicians encouraged it. A multipage glossy ad campaign that ran frequently in the *Annals of Internal Medicine*, for example, featured a thin, 40-something white woman with a crumbling ancient stone column in the background. "Don't wait for a fracture. . . . No matter what her degree of osteoporotic bone loss."[16] I wrote to the editor-in-chief of *Annals*, pointing out that alendronate had no proven benefit in women in early middle age or in those without a history of fracture. I never received a reply, but the journal stopped running the ad about six months later.

Still, the message had already gone out, there and elsewhere—early middle age is the appropriate time to start fracture prevention with alendronate. From the drug industry's point of view, the younger customer is far more desirable than, say, an older nursing home resident with a limited number of years left in which to take the drug. Today, women in the osteoporosis drug ads are usually in their early 60s. The 2002 guidelines for osteoporosis screening from the Agency for Healthcare Research and Quality recommend that bone-density scanning not begin until age 65 (or 60 in some high-risk cases).[17] Researchers have known, at least since 2000, that *bone strength* or *bone quality* are better predictors of hip fracture than *bone density*. In 2001 the National Institutes of Health redefined osteoporosis as a combination of bone strength and bone quality. But there is no test for bone quality or bone strength, and many physicians continue to base their prescribing decisions on bone density, the one thing they can measure. It's going to take time for the word to get out.

OTHER DRUGS, SAME STORY

How relevant is the bisphosphonates story to that of other drugs people take to treat a risk factor? In a word: *very*. Three-fourths of all Americans on cholesterol-lowering statins, the country's top-selling drugs, do not have heart disease and are thus far less likely to benefit than people who do.[18] (Statins are terrific at lowering cholesterol, but much less impressive when it comes to the ultimate goal of reducing heart attacks and strokes[19]—sound familiar?) The threshold for high cholesterol has been lowered several times over the years, each time making millions more people eligible for drug therapy.[5, 20]

MANY PHYSICIANS CONTINUE TO BASE THEIR PRESCRIBING DECISIONS ON BONE DENSITY, THE ONE THING THEY CAN MEASURE.

Drug ads and industry-sponsored "education" programs are no longer the only major sources of biased information. Industry funding compromises the directives of nonprofits like the American Heart Association and the American Cancer Society, as well as the experts who write treatment guidelines.[21] One example of the latter: eight of the nine doctors who served on the 2004 government committee that expanded the guidelines for cholesterol-lowering drug therapy had financial ties to statin companies.[22] More than ever, nurses must be knowledgeable advocates for their patients. You may be the last of the independent health care professionals. ▼

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