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A Crisis in the Treatment of Osteoporosis

The field of osteoporosis may be coming full circle, and that is not good for the millions of older women and men who will suffer painful and disabling spine and hip fractures—fractures that might have been prevented. As physicians, we are now watching as the fundamental progress made to reduce fractures and dramatically improve the quality of life of our patients during the past 30 years unravels.

Osteoporosis was long considered an inevitable consequence of aging, in which the typical scenario played out with remarkable consistency: "Grandma" developed the characteristic "dowager's hump," later fractured her hip, was forced to leave her home and languish in pain and immobility in a nursing home, where she finally succumbed to the complications of that existence with a premature and avoidable death. However, over the course of the lifetimes of at least some of us, the scientific and medical community made remarkable advances in the diagnosis and treatment of osteoporosis.

Epidemiological studies clearly defined the patterns and risk factors for age-related bone loss. Systematic studies conducted in animals and in humans defined the mechanisms of bone loss due to estrogen deficiency, aging, glucocorticoids, and many other factors. These fundamental advances in the understanding of the pathogenesis of osteoporosis drove the development of new treatments including estrogen, SERMs, teriparatide, and denosumab, with abaloparatide, romosozumab, and odanacatib on the horizon. The field also benefited by the fortuitous discovery that bisphosphonates, which were originally developed for other purposes,[1] also turned out to disable osteoclasts and were developed into the most widely-used drugs today to prevent and treat osteoporosis. In 2016, we should be celebrating these triumphs of science and medicine because, by these criteria, we have made remarkable progress toward our goal of markedly decreasing the burden of a devastating disease. We should be viewing the future for our patients with osteoporosis with unparalleled optimism, because we now have several drugs that can substantially reduce fracture incidence, by as much as 70% in the case of vertebral fractures.[2] Thus, although physicians still struggle to treat many other conditions that are currently intractable, including Alzheimer's disease and many cancers, the good news is that the prevention of fractures is clearly within our reach. And yet, despite the development of several effective drugs to prevent fractures, many patients, even those who unequivocally need treatment, are either not being prescribed osteoporosis medications at all, or when prescribed, refuse to take them.

This paradox has been brewing for some time, but the issue was brought to a head by a recent article by Gina Kolata in the *New York Times* titled, "Fearing Rare Side Effects, Millions Take Their Chances with Osteoporosis."[3] This article, which garnered considerable attention in both the medical and lay community, was based, in part, on a paper by Jha and colleagues.[4] published recently in the *JBMR*. Using an ecological analysis of media reports, oral bisphosphonate use, and fracture outcomes in the United States, the authors demonstrated a series of spikes in Internet search activity for alendronate between 2006 and 2010 immediately following media reports of safety concerns: specifically, osteonecrosis of the jaw (2006), atrial fibrillation (2008), and atypical femur fractures (2010). Coincident with media and public concern about these rare side effects, bisphosphonate use declined by greater than 50% from 2008 to 2012. Admittedly, some of this decline may reflect an appropriate response to advances in medical knowledge which helped clarify that bisphosphonates have limited efficacy in patients who are at low "short-term" risk of fracture.[2] Other patients were stopped, also appropriately, because they had been on these drugs for many years, and evolving information helped us to recognize not only that osteonecrosis of the jaw and atypical femur fractures were associated with long duration of use, but also that the benefits of prolonged therapy were uncertain.[2] However, there is increasing recognition that this decline also reflects the fact that many patients who clearly need osteoporosis therapy are not receiving it.

This concern was confirmed by another recent study that used claims data from a U.S. commercial health plan (2004–2013) to evaluate the impact of U.S. Food and Drug Administration (FDA) announcements related to the potential risks of bisphosphonates on their use in patients with hip fracture.[5] Although there are certainly controversies in the field of osteoporosis, there are also issues upon which there is complete or near-complete agreement: specifically, there is consensus that patients with hip fracture should receive pharmacological treatment to prevent additional fractures, because they are clearly at risk for recurrent hip or other osteoporotic fractures, and initiation of bisphosphonate therapy after hip fracture has been shown to reduce the risk of a second hip fracture.[6] Despite consensus on this issue, the authors found that among 22,598 patients with hip fracture, use of bisphosphonates decreased from an already dismal 15% in 2004 to an abysmal 3% in the last quarter of 2013. To draw an analogy from another field, in 2016 it is virtually inconceivable that a patient discharged from the hospital following a myocardial infarction would not be prescribed a full armamentarium of drugs for secondary cardiovascular prevention (eg, a statin, antihypertensive, and others). Yet what is inconceivable for a

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patient following a myocardial infarction is the norm in the vast majority of patients discharged from hospital after a hip fracture.

The scope of the problem may, in fact, be even worse because Jha and colleagues[4] used prescription databases and could not evaluate patient compliance. Indeed, adherence to oral bisphosphonates is low, and estimates are that less than 40% of patients who are prescribed these medications are still taking them after 1 year.[7] Consistent with this, most of us in practice have observed that a significant proportion of the patients we see clinically are reluctant to initiate bisphosphonate therapy and many on these drugs want to stop taking them and do so despite our best advice. Furthermore, because atypical femur fractures have now been reported, albeit at very low frequencies, not only with bisphosphonate use but also following treatment with denosumab,[8] romosozumab,[9] and odanacatib,[10] patients are becoming increasingly reluctant to take any osteoporosis drug. Thus, the collective body of epidemiological and anecdotal evidence is now compelling: patients with osteoporosis who clearly need therapy are either not being offered appropriate medications or are simply not taking these medications.

How did our field arrive at its current situation? Are we, for example, suffering the backlash from critical media reports, such as the one by NPR's Alix Spiegel in 2009 entitled, "How a Bone Disease Grew To Fit The Prescription,"[11] which claimed that the pharmaceutical giant, Merck, created the disease of "osteopenia" in order to expand the sales of their newly released drug, Fosamax? In our defense as osteoporosis physicians, when bisphosphonates were initially approved, we used them (particularly alendronate at a lower, "prevention" dose) to prevent the irreversible deterioration in skeletal microarchitecture that leads to osteoporotic fractures, much as statins are now being widely used to prevent cardiovascular disease that leads to myocardial infarction. A second problem could be that when patients only hear about relative risks and not absolute risks, all sense of proportion may be lost. As such, have we, as a community of "experts," failed to communicate clearly to the public the benefits versus the risks of osteoporosis therapy? For example, based on an analysis of three randomized controlled trials of bisphosphonates, treating 1000 women with osteoporosis for 3 years with a bisphosphonate will prevent approximately 100 vertebral or nonvertebral fractures (number needed to treat: 10).[12] These numbers compare very favorably with the numbers for statin therapy, which indicate that treating 1000 people with a statin for 5 years will prevent approximately 18 major cardiovascular events (number needed to treat: 56).[13] Importantly, for the 100 fractures prevented, bisphosphonates might cause 0.02 to 1.25 atypical femur fractures, assuming the relative risk ranges from 1.2 to 11.8 (number needed to harm: 800 to 43,300).[2] Yet our patients are dismissing these medications out of hand and deciding to "take their chances" with fractures. This compels the last question—have we also failed to adequately educate the public about the devastating consequences of osteoporosis—the loss of mobility and markedly reduced quality of life following vertebral fracture and the likely death-spiral following hip fracture? Our record compares poorly with, for example, the widespread awareness among women of the devastating complications and mortality related to breast cancer and the appropriate, widespread use of early detection and better patient compliance with the treatment of that disease.

In short, we, as physicians who care deeply about the treatment of patients with osteoporosis, find ourselves in a dire situation. At a point in time when we have developed pharmacologic tools capable of preventing enormous suffering and needless mortality, we may well be coming back full circle: the downward spiral of vertebral fracture, hip fracture, immobility, loss of independence, and premature death that we thought we had conquered may soon become the accepted norm again. There can be no more urgent call to action for our field than we face today. We must find ways to ensure that patients who need appropriate treatment for osteoporosis are not only prescribed effective medications, but are also equipped with the information they need to make an informed choice on taking these medications. What the next steps should be are not obvious, but we may well need help from others, because in one way or another we may all be perceived to be conflicted. Because of this perception, the public may simply choose to ignore our task forces, white papers, and reports. It will take a concerted effort involving our colleagues at NIH, the U.S. Surgeon General's Office, CDC, and other national and international agencies, to help us in this important effort. If we fail, all our efforts—for some of us, our life's work—will have been for naught. Although we could individually bemoan this loss, that would be self-serving. The only issue that really matters is that we would have failed our patients, and that is something we cannot allow to happen.

Disclosures

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