Underdiagnoses and Undertreatment of Osteoporosis: The Battle to Be Won

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Postmenopausal osteoporosis is underdiagnosed and undertreated. In part, this observation is related to declining reimbursement for dual-energy x-ray absorptiometry testing and underappreciation for the high fracture risk associated with vertebral compression fractures as well as hip fractures. Failure to appropriately manage skeletal health after the first fracture in order to prevent a second fracture is a gap in our management of osteoporosis that leads to undertreatment. In addition, there is fear among both patients and physicians concerning certain pharmacological therapies for osteoporosis and their associations with atypical subtrochanteric femur fractures (AFFs). The scientific data associating bisphosphonate use and the development of AFF is mostly retrospective epidemiological data, much of which is confounded by indication. Furthermore, a substantial proportion of AFFs occur without any bisphosphonate use. A U.S. Food and Drug Administration advisory panel convened September 9, 2011, also concluded that data were inadequate to truly support restricting the duration of bisphosphonate use for patients requiring long-term bisphosphonate treatment for osteoporosis, and panelists were not confident that implementing a drug holiday or discontinuing bisphosphonate use after a period time would be beneficial. The long-term bisphosphonate extension studies also validated the hypothesis that discontinuing bisphosphonates after 3-5 years of use was not associated with consistent fracture protection, even for elderly patients with World Health Organization dual-energy x-ray absorptiometry-defined osteopenia without prevalent vertebral compression fracture. Older patients (age ≥ 69 y) even with osteopenia and no prior fractures should be continued on osteoporosis therapies, and patients should be counseled on the poor evidence of an association between bisphosphonate use and the risk for AFF vs the strong evidence documenting the protection by treatment on the reduction of typical hip fractures. (J Clin Endocrinol Metab 101: 0000-0000, 2016)

"The whole art of war consists in getting what is on the other side of the hill," Duke of Wellington commenting on The Battle of Waterloo, June 15, 1815.

Osteoporosis is, for those of us devoted to abolishing this disease, the battle being lost on many faces of many hills. Paul D. Miller, M.D. September 26, 2015.

Osteoporosis is both an underdiagnosed and undertreated disease (1). The annual cost in the United States of caring for osteoporotic-related fractures parallels or exceeds the annual cost for myocardial infarction, breast cancer, and/or cerebrovascular accidents (2, 3) (Figure 1) (4). In addition, in a large study in Manitoba, Canada, the ratio of the total annual costs of either prevalent or incident osteoporotic-related fractures exceeds the same ratio calculated for many other serious chronic diseases (5). Equally disturbing are data showing that the percentage of patients receiving a registered therapy for osteoporosis, even after sustaining a hip fracture, has declined in the United States from 41% in 2001 to 21% in 2011 (Figure 2) (3). Finally, the leading cause of the loss of independence in men or women 70 years of age and older is fractures due to falls at home (6-8).

Abbreviations: AFF, atypical subtrochanteric femur fracture; DXA, dual-energy x-ray absorptiometry; MOA, mechanism of action.
Osteoporosis Is Underdiagnosed and Undertreated. Why?

There are many opinions regarding the decline in the diagnosis and treatment of osteoporosis. In this author’s opinion, the three major reasons are:

1. The decline in bone mineral density testing by dual-energy x-ray absorptiometry (DXA) in non-facility-designated DXA sites (eg, private practices) (9-12).
2. The underappreciation of the seriousness of all osteoporotic fractures, including asymptomatic vertebral compression fractures, and the failure to ensure that patients admitted to hospital facilities with osteoporotic fractures are directed into an osteoporosis management plan to prevent a second fracture (13-19).
3. The fear that has been imbued in the minds of patients as well as many physicians concerning the safety of bisphosphonates, eg, their association with osteonecrosis of the jaw and/or atypical subtrochanteric femur fractures (AFFs) (20, 21).

Medicare reimbursement for DXA at nonfacility institutions has declined since 2007 when DXA testing was bundled into a larger Congressional bill to an unsustainable average of approximately $37 per test, whereas facility (hospital and free-standing radiological center) reimbursement has either remained the same or increased ($100/test) (9-12, 22, 23). This current policy is both unfair and discriminatory. The International Society for Clinical Densitometry (ISCD) and multiple other professional societies involved in osteoporosis patient management and research have recently supported a bill in Congress (Increasing Access to Osteoporosis Testing for Medicare Beneficiaries Act of 2015, HR 2461, 114th Congress) to set a flat and common floor for all DXA providers nationwide of $98/test (24). There is also a large imbalance in costs for osteoporosis management. One example is the measurement of serum 25-hydroxyvitamin D, an important test for osteoporosis management that is reimbursed at approximately $200, whereas payment for DXA, a test with wide applications for diagnosis, risk assessment, and monitoring of treatments, has a meager payment that is two-thirds lower than the payment needed just to break even on the cost of doing DXA.

Vertebral compression fractures are the most common form of osteoporotic fractures. Most of these are asymptomatic (13, 14). However, both clinical (painful) and asymptomatic (radiographic defined) vertebral compression fractures increase the risk of not only more clinical and asymptomatic vertebral compression fractures but also nonvertebral fractures (13, 14, 17, 25-31). Morphometric vertebral compression fractures that are not related to any historical recall of trauma and may not be able to be dated as to when these “silent” fractures occurred are symbolic of systemic skeletal fragility. This increased risk of all systemic fractures in untreated postmenopausal or male patients with silent vertebral compression fracture is the single most important missed opportunity to impact osteoporosis at the primary care level. The occurrence of any fragility fractures, with the exception of fractures of the hands, feet, or skull, is the single greatest risk factor for the development of a second fragility fracture in untreated patients (32-35).

The international movement to develop Fracture Liaison Services (FLS), spearheaded in the United States by
The National Osteoporosis Foundation (NOF) and The National Bone Health Alliance (NBHA) and internationally by The International Osteoporosis Foundation (IOF), is a multidisciplinary effort to reduce the incidence of the second osteoporotic fracture (7, 18, 36). The FLS relies on developing mechanisms and pathways to identify patients admitted to hospitals, emergency rooms, or urgent care clinics with osteoporotic fractures and direct those patients into a well-developed osteoporotic management and treatment plan. However, funding for a designated professional to implement and coordinate FLS programs has been inadequate to document a successful track record and the impact on recurrent fractures at this time.

The large media-driven attention given to the association of bisphosphonate use and AFFs has been a factor in the declining acceptance of therapies for osteoporosis (37, 38). The first national media attention given to the issue of bisphosphonates and AFFs was in the American Broadcast Corporation’s (ABC) story on March 10, 2010, suggesting that the manufacturer of alendronate knew about the relationship between alendronate use and the development of AFF, a statement that even to this day has been invalidated. After that broadcast, practitioners in the field of osteoporosis care witnessed a growing unacceptance of bisphosphonates and, ultimately, osteoporosis therapies in general. Additionally, direct consumer marketing, especially in television advertisements, seems to overemphasize the risks of approved therapies for osteoporosis while understating their benefits. Patients become fearful rather than hopeful. In this environment of negativity, inflammatory articles appear that fuel hysteria even among professionals to the point that frankly state that the medical community itself overstates the seriousness of osteoporosis (39–41). This type of irresponsible journalism and absurd papers does nothing constructive to support the undertreatment of osteoporosis. Many highly respected professional societies have written well-documented and peer-reviewed articles pointing out the honest facts about the seriousness of osteoporosis (42).

Subtrochanteric femur fractures represent approximately 10% of the total number of osteoporotic-related low trauma femur fractures that occur annually in the postmenopausal population (43). The term “atypical” subtrochanteric femur fracture was coined by several investigators to describe a specific type of subtrochanteric femur fracture (44, 45). The features that discriminate a subtrochanteric fracture as being atypical are articulated in the American Society for Bone and Mineral Research (ASBMR) working group reports on AFF (46, 47). It is important in both the ASBMR task force papers and separate publications on AFF, that AFFs may, and often do, develop independent of bisphosphonate exposure; they may also be seen in other clinical situations with risk factors for AFF independent of bisphosphonate use, including diabetes, glucocorticoid use, protein pump inhibitor use, adult hypophosphatasia, or lower extremity fracture syndrome observed in otherwise healthy premenopausal women (48). The term “AFF” was actually created before the 2008 ASBMR scientific meeting where credit is often given to investigators for describing the unique radiological features that make a subtrochanteric femur fracture atypical (43). In fact, the radiological descriptive features defining an AFF were reported even before bisphosphonates were marketed in the United States (49–54).

There have, however, been an increasing number of AFFs reported in epidemiological studies since the approval of bisphosphonates for postmenopausal osteoporosis in 1995 (54–59). Multiple professional societies involved in bone metabolism have stated that causality between AFF and bisphosphonates has not been established. Other epidemiological studies that have controlled for baseline risk for the development of bisphosphonates and AFF have not even found an association between the two (60). No mechanism of action (MOA) has been val-
idated as to just how bisphosphonates may induce an AFF. It is also possible that the apparent increase in AFFs occurring in subjects on bisphosphonates has nothing at all to do with bisphosphonate exposure because the very individuals that are at high risk for developing these forms of femur fractures (low bone mass) are the same subjects who may be selected to receive bisphosphonates, eg, the data is confounded by indication.

Most femur fractures that occur in the osteoporotic population are “typical.” That is, they are located above the lesser trochanter, either in the femoral neck or between the greater and lesser trochanters (“intertrochanteric”), and occur after falls. AFFs derive their definition by three means (47):

1. They occur with little or no trauma.
2. They are lower in the femoral shaft, below the lesser trochanter.
3. They have specific radiological characteristics that help define the radiological criteria.

There are plausible reasons why causality has not been confirmed in attributing the occurrence of AFF to bisphosphonate exposure:

1. No MOA whereby bisphosphonates might induce AFF has ever been scientifically defined.
2. Bisphosphonate uptake in the femur shaft area where AFFs begin is extremely small because these areas of cortical bone have annual bone turnover rates of approximately 1% per year, in contrast to cancellous bone where bisphosphonate uptake is greatest at approximately 30% per year (61–64).
3. Bisphosphonate exposure cannot explain the AFFs that occur without any bisphosphonate exposure (21, 65, 66).
4. Bisphosphonate exposure cannot explain the AFFs that are seen with other conditions that may affect bone quality (67, 69).
5. No altered biomechanical examinations have ever provided a scientific answer linking bisphosphonate exposure to impairment in bone strength or bone quality (63, 69–72).

Bisphosphonates reduce bone remodeling, which is one of the mechanisms whereby they increase bone strength and reduce fracture risk. They may have other MOAs independent of reduction in alterations in remodeling that also contribute to the improvement in bone strength (49, 52, 63, 72). Bisphosphonate use in clinical trials has never been shown to “shut off” bone remodeling or to maintain bone turnover, which may be defined by biochemical markers of bone turnover, especially the bone resorption marker C-telopeptide, consistently below the defined pre-menopausal normal reference range (73–77). However, it has been suggested that suppression (or “oversuppression of bone turnover”) may be a MOA for how bisphosphonates may induce AFF. In a previous report, we documented using quantitative bone histomorphometry that eight of 15 patients with bisphosphonate-associated AFF had no single or double tetracycline labels, meaning that their bone turnover was unmeasurable at the standard site for performing transiliac bone biopsies, the iliac crest (78). However, the other seven patients had bone turnover rates that were measurable and had tetracycline labels, although the mean values were below the average normal turnover rate for the healthy premenopausal population (79). In a forthcoming, separate, more robust analysis of 14 patients receiving long-term bisphosphonates who developed AFF, bone biopsies also did not show absent tetracycline labels (86). Hence, it does not appear that “oversuppression” is a viable mechanism for linking AFF to bisphosphonates.

Nevertheless, the fundamental reason that the U.S. Food and Drug Administration (FDA) held an advisory board meeting on September 9, 2011 (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM278481.pdf) was to consider a change in the FDA bisphosphonate labeling to define a restricted duration of use. This restriction was predicated on three points:

1. The inadequate long-term efficacy data of bisphosphonate use, eg, that there are limited data on continual fracture benefit beyond 5 years.
2. The unique pharmacology of bisphosphonates (not metabolized, retained in bone, and recycled) would allow temporary discontinuation of bisphosphonates while preserving some of their biological effect.
3. The assumption that there exists a link between bisphosphonate duration of use and the risk of AFF.

The first issue, a lack of evidence for long-term efficacy, is not well justified due to the small sample sizes in bisphosphonate extension studies and the inability to maintain the original randomized registration clinical trial placebo population for an extended period of time. The first assumption may never be validated in higher-risk populations.

The second critique is, in part, biologically correct. Bisphosphonates do retain some pharmacological effect after discontinuation, although the data supporting the maintenance of fracture reduction is based on small sample sizes of extension data from two bisphosphonate clinical trials (the FLEX trial, “Fosamax long-term extension”; and the HORIZON trial, the 3-y extension of the original zoledronic acid registration study) (80, 81). De-
spite the noble attempts to provide long-term data, both studies fall short of being able to provide sufficient evidence for protection of fractures after discontinuation. FLEX is the larger of the two extension studies, but it is a subset (n = 1099) of the original alendronate fracture intervention registration trials (n = 6459). During FLEX, for patients in the placebo group who prior to FLEX had been on alendronate for approximately 4.5 years, bone mineral density declined, and biochemical markers of bone turnover increased, inconsistent with the proposed prolonged pharmacological effect of bisphosphonates; clinical vertebral fractures significantly increased in the placebo ("off therapy") group. There were no interactions between either the baseline T-score (down to −2.0 at the femoral neck) or prevalent vertebral fractures and the ability to predict which patients off therapy would sustain another clinical vertebral fracture. FLEX offers little evidence for consistent maintenance of a clinical effect after discontinuation for fractures at all skeletal sites.

The third critique, that there exists a significant interaction between the duration of bisphosphonate use and the development of AFF, is based on weak data (82). In addition to the previously cited data showing the substantial proportion of AFFs occurring in patients not receiving bisphosphonates, the duration data are based on retrospective epidemiological data, much of which may be confounded by indication, and the cited pivotal, also retrospective, study used to validate that there is an incidence rate for the development of bisphosphonate-associated AFFs (82). This latter analysis is not a true incidence rate. A true incident rate should have as the denominator the number of patient-year exposures (total cohort, total exposure) rather than duration of bisphosphonate exposure as was reported (83).

With this knowledge concerning the limitations of the bisphosphonate AFF interaction data, the FDA advisory panel provided its recommendations concerning a potential change in the FDA bisphosphonate label. The panel did not support restricting the duration of use (Table 1) (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/) , a position on which the FDA later took issue and published its own opinions (84). The FDA advisory panel was correct. The long-term bisphosphonate data are inadequate to recommend stopping therapy, especially in specific populations of elderly people (age ≥ 69 y in FLEX) where the long-term bisphosphonate data do not show complete fracture protection at all skeletal sites in patients taken off bisphosphonate. Most clinicians do not stop treatment for most other chronic diseases, where the pathophysiology for the disease process continues (e.g., diabetes mellitus, hypertension, chronic obstructive pulmonary disease) unless the underlying cause of the disease can be corrected. Why should we consider "drug holidays" from bisphosphonates in specific, especially elderly patients when the basic mechanism for the disease persists? This author would not argue against discontinuation with this unique pharmacological class of agents (bisphosphonates) in younger patients; however, the data that we do have indicate that elderly patients even without osteoporosis by T-score or the presence of a vertebral fracture are protected against subsequent fractures during bisphosphonate "holidays."

In this author's opinion, the fear that pervades both patients and physicians is that bisphosphonates cause AFF, and the incorrect belief that they continue to protect against all fractures after discontinuation is the main driver causing the undertreatment of even severe osteoporosis. Certainly, the unsustainable DXA reimbursement rate has a role as well.

**Conclusion**

The underdiagnosis and undertreatment of osteoporosis represents a substantial health care problem. Few other chronic diseases have received the unacceptance of therapies to the magnitude that pervades osteoporosis care. Unified positions among professional societies involved in the care of patients with osteoporosis are needed, as well as clearer messages. The recent work by the NBHA on clarifying the clinical diagnosis of osteoporosis is a start to this process (85). In addition, all professional societies

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**Table 1.** A Few Key Points From the Advisory Board of the September 9, 2011, FDA Hearing on Bisphosphonate Duration of Use

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<th>Summary Minutes of the Joint Meeting of the Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee</th>
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<td>&quot;...no data to truly support that restricting the duration of use was beneficial for patients requiring long-term bisphosphonate treatment for osteoporosis&quot;</td>
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<td>&quot;...the committee recommended that the label should further clarify the duration of use for bisphosphonates&quot;</td>
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involved in osteoporosis need to unite and demand more responsible and balanced media reporting and a re-examination of the impact of direct consumer marketing by pharmaceutical companies on patients’ perceptions of benefit/risk of our osteoporosis therapies. Critically examining and articulating the data and pointing out the limitations of the data will be a starting point in reversing the downward spiral in the trust of therapies for osteoporosis. The very high benefit-to-risk ratio of our interventions needs to be the starting point. This is true for all diseases we treat and is especially true for higher-risk osteoporotic patients where the benefit-to-risk ratio for the reduction in the risk of a typical hip fracture with bisphosphonate use far exceeds the risk of the occurrence of an AFF (49, 52).

We, as a committed body of professionals, are losing the battle against one of the most serious diseases mankind faces in an aging population. Gaining control of the battlefield, as Wellington did with the help of an army of internationals, can be done, but it starts with recognizing some of the key flanks we have to take to regain control of the battle. The ASBMR, NOF, IOF, NHTHA, ISCD, and other international forces can conquer these flanks if they work together. These flanks have been articulated in this opinion article.

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