A New Look at Osteoporosis Outcomes:
The Influence of Treatment, Compliance, Persistence, and Adherence

Osteoporosis is a disease in which excessive bone resorption leads to reduced bone mass and skeletal fragility, the most significant clinical outcome being increased risk of fracture. An estimated 10 million Americans have osteoporosis (8 million women and 2 million men). The average 50-year-old woman has a 40% lifetime risk of osteoporotic fracture. Fractures, especially hip fractures, lead to increased mortality and morbidity and reduced quality of life. Hip fractures are also the largest contributor to health care costs associated with osteoporosis in the United States.

Currently approved therapies for osteoporosis in the United States include bisphosphonates (primarily alendronate, risedronate, and ibandronate); hormone replacement therapy (HRT); a selective estrogen receptor modulator, raloxifene; calcitonin; and teriparatide. The literature suggests that adherence with osteoporosis medications in clinical practice is about 60%. Discontinuation rates are particularly high during the first year. More troubling, as the article by Siris et al in this issue of Mayo Clinic Proceedings demonstrates, is that poor adherence is associated with negative outcomes, including increased fracture risk.

For a chronic condition such as osteoporosis that requires long-term therapy, it is important to understand how patient drug-taking behavior influences patient health outcomes and health care expenditures. Compliant patients take their medication as instructed. They take it with the proper frequency and at the correct time(s) of day, with or without food and/or other medications or supplements as necessary. Persistence refers to the duration of time during which a medication is taken. Adherence comprises compliance and persistence (Figure 1) and refers to taking medications as instructed during a given period. Adherence is typically estimated by the medication possession ratio (MPR). The MPR is determined by examining prescription refill data to assess how much medication was available to take for a given period. If a certain medication is prescribed for daily use, a patient would need to have 60 pills to take over 60 days to have an MPR of 100%. In real life, a patient may not refill the prescription before the first prescription has run out. Thus, if 2 weeks elapsed before the prescription was refilled, the MPR would be 81% (60 pills per 74 days). The MPR is limited in that it does not provide insight into consistency of refilling or whether a drug is being taken as directed; however, it is currently one of the most widely used measures to approximate drug-taking behavior of patients.

Less than optimal adherence with osteoporosis therapy is not a new phenomenon. Studies published in the early 1990s estimated that adherence with HRT for osteoporosis was about 70% among those who actually started therapy. Since the publication of results from the Women’s Health Initiative, fewer women take HRT, but recent studies indicate similar rates of adherence. Adverse effects such as bleeding are the most common reason given for discontinuing HRT. Numerous studies have shown that adherence with bisphosphonates and raloxifene is about 55% to 65%. These drugs demonstrated efficacy in increasing bone mineral density (BMD) and decreasing fracture risk in clinical trials in which adherence was closely monitored. Although it was assumed that effectiveness would be somewhat reduced in the real-world setting because of differences in patient adherence, it was only recently that researchers began to define the outcomes associated with low adherence.

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Yood et al24 evaluated 176 women in a primary care setting. All had initial BMD measurements and a diagnosis of osteoporosis. About half the women were prescribed estrogen, and half were prescribed bisphosphonates (>90% received daily alendronate and the rest received etidronate). Women were contacted a year after their initial BMD measurement and invited to return for a follow-up BMD measurement. About half were willing to undergo a second BMD test. Overall adherence with therapy was 70% and was similar among those who returned for follow-up and those who did not. Among the women who had a second BMD test, those with an MPR of 66% or greater (as determined from a pharmacy claims database) had a significantly greater increase in BMD than those who were less adherent (MPR, <66%). This study was among the first to explore the association of adherence with a relevant clinical outcome.

Two studies used pharmacy claims databases to evaluate adherence and outcomes in larger numbers of patients. Caro et al25 followed up more than 10,000 Canadian women for 2 years. The average MPR during the period of follow-up (mean length, 2 years) was approximately 70%, and less than one half of patients had an MPR of 80% or higher. Furthermore, 40% of patients had discontinued treatment by the time the follow-up period ended. A multivariate analysis that controlled for age, prior fractures, and prior use of osteoporosis medication or corticosteroids demonstrated an associated 16% reduction in fracture risk for patients with an MPR of 80% or higher compared with less adherent patients. A consistently high level of adherence (≥90%) was needed for an optimal reduction in fracture risk because all other categories of adherence were associated with a significantly increased risk of fracture compared with this group. McCombs et al5 found 1-year compliance rates in 58,000 US women to be less than 25% for all osteoporosis therapies examined (HRT, bisphosphonates, raloxifene), using a 14-day refill window as a measure of persistence. The MPR ranged from 61% to 81%. Uninterrupted therapy for 1 year was associated with a significantly reduced risk of both hip and vertebral fractures compared with patients who discontinued or interrupted therapy. Furthermore, patients with uninterrupted therapy for 1 year used significantly fewer physician and hospital outpatient services.

In their study of more than 35,000 women, Siris et al10 extended the observations made by Caro et al25 and McCombs et al.3 This retrospective cohort study used a large, integrated administrative medical and pharmacy database to identify women 45 years and older who had been prescribed a bisphosphonate from July 1999 to December 2001. Patient claims during a 2-year period after the index prescription were reviewed, and the association between adherence with therapy and fracture risk was determined. Using an MPR of 80% or higher as an indicator of adherence, 43% of women were considered adherent over a 2-year period, with a 21% reduction in fractures overall compared with women who were nonadherent (MPR, <80%; P<.001). The relative risk of fracture in adherent patients was also significantly lower for vertebral fractures, all nonvertebral fractures, and hip fractures but not for wrist fractures. Persistence was poor, with 80% of women having at least 1 gap of more than 30 days between medica-

![Figure 1. Persistence refers to the duration of time during which a medication is taken. Compliance is the proportion of medication taken at a given time according to instructions while persistent. Adherence represents compliance over time and can be estimated within discrete periods using the medication possession ratio.](image)
tion refills during the 2-year period. The overall fracture rate was 29% lower for women without a refill gap than for those who were not persistent with therapy. The diagnosis of osteoporosis did not improve adherence rates. Adherence in a subpopulation of patients (18%) who had a specific diagnosis of postmenopausal osteoporosis during the study period was similar to adherence in the overall population.

Of importance, Siris et al estimated the probability of fracture along a gradient of adherence. At an MPR from 0% to 50%, the probability of fracture during a period of 24 months remained consistent at about 11%. With an MPR greater than 50%, the probability of fracture decreased as adherence increased. These results are supported by a recent study by Huybrechts et al that found similar results. In that study of 38,000 women taking osteoporosis medication between 1997 and 2002, 26% had an MPR of at least 80% during a mean follow-up of 1.7 years, with the sharpest decline in adherence occurring during the first year with adherence then becoming stable with a gradual decline. As adherence decreased to below 90%, fracture risk increased significantly. Relative risk of fracture in patients with 80% to 90% adherence was 9.1% higher than in those with adherence greater than 90%, whereas relative risk of fracture in patients with less than 50% adherence was 21% higher than in those with adherence greater than 90%. The study by Huybrechts et al also showed that small reductions in adherence were associated with higher hospitalization rates and increased costs.

The factors that influence adherence are many, some of which are amenable to interventions. These include the type and stage of disease, cost, frequency and complexity of the dosing regimen, medication adverse effects, age, mental state, acceptance and understanding of the illness, and in the case of osteoporosis specifically, BMD testing and prior fracture. Although most studies of adherence with osteoporosis therapy have found significant differences between patients who are and who are not adherent, these factors are not always consistent among studies, and attempts to develop a predictive model have been unsuccessful. In a recent study, variables such as age and prior BMD testing accounted for only 6% of the variation seen in adherence levels. Associations of prior fracture with adherence have been inconsistent.

The study by Siris et al conducted from 1999 through 2003, which includes the time when weekly bisphosphonate formulations became available; thus, patients taking daily and weekly bisphosphonate therapy are included in the analysis. Several recent studies suggest that 1-year adherence and persistence rates for oral bisphosphonates are better with once-weekly therapy than with daily therapy, although they remain suboptimal.

The study by Siris et al does not indicate what proportion of patients were receiving daily vs weekly bisphosphonate therapy or whether there were differences in fracture outcomes between these 2 groups.

Siris et al conducted their study using a health care claims database, which has inherent limitations. Because these databases are set up for the purposes of cost, they do not necessarily contain all the relevant clinical information, such as BMD values and full patient histories. Furthermore, coding errors may cause imprecision in determining fracture rates. Nonetheless, claims databases have been found to be a reliable estimate of patient use of medications.

Although the low adherence rates with osteoporosis therapies and associated risks of fracture are troubling, improved outcomes may be obtained with marginal increases in adherence. An improvement from the current rate of about 60% to adherence of 80% may substantially reduce fracture risk and health care costs. Thus, pursuing interventions that could improve adherence is worthwhile. The addition of new medications for osteoporosis with more convenient dosing schedules may help to improve adherence. The development of interventions that can be used by the practicing physician to engage patients in the treatment of their disease may also be beneficial.

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