Review of Adherence to Medications for the Treatment of Osteoporosis

Deborah T. Gold, PhD, and Stuart Silverman, MD, FACP, FACR

Corresponding author
Deborah T. Gold, PhD
Departments of Psychiatry & Behavioral Sciences, Sociology, & Center for Aging, Duke University Medical Center, Box 3003, Durham, NC 27710, USA.
E-mail: dtg@geri.duke.edu

Current Osteoporosis Reports 2006, **4:**21–27
Current Science Inc. ISSN 1544-1873

One of the major challenges of successful osteoporosis management is poor patient adherence to current therapies. Individuals who are nonadherent have significant consequences of reduced bone mineral density response, reduced bone marker suppression, and increased risk for fracture compared with individuals who are adherent. Although reducing the dosing interval from daily to weekly oral bisphosphonates has improved adherence, adherence with weekly bisphosphonates remains suboptimal. Barriers to adherence include patient health beliefs, inadequate patient education and age. Potential solutions include increased health care provider-patient interaction, and longer times between doses of medications.

Introduction

During the past decade, "osteoporosis" has been transformed from a clinical term describing an obscure metabolic bone disease to a household word. This change was made possible, at least in part, by facilitated access to state-of-the-art diagnostic technology for evaluating changes in bone density (dual-energy x-ray absorptiometry [DXA]). In addition, a wide variety of therapies have been approved by the Food and Drug Administration (FDA) since 1995 to prevent bone loss, reduce the risk for fractures, and/or supplement the growth of new bone.

Given the number of osteoporosis drugs that are currently available, or being tested in the pipelines of major pharmaceutical companies, and the overwhelming evidence supporting the efficacy of marketed agents, we might expect that preventing and treating bone loss would be simple and generally successful. Unfortunately, adherence to all osteoporosis medications has been extremely poor. In fact, improving patient's adherence to osteoporosis therapies may be the single most important health-related behavioral challenge facing professionals who diagnose and treat this disease. To find solutions, it is imperative to understand why patients do not adhere to prescriptions written for anti-osteoporosis medications.

In this paper, we discuss rates of adherence to medications in general, adherence to therapies that are specific for osteoporosis, and reasons underlying poor adherence. We conclude by suggesting strategies for helping physicians to design appropriate care plans and collaborate with their patients to select osteoporosis medications and dosing regimens most likely to be followed.

What Are Adherence, Compliance, and Persistence?

Before further exploring patience adherence to osteoporosis medications, three words need to be defined—compliance, persistence, and adherence. These words are consistently used interchangeably in much of the literature, despite differences in their meanings. Compliance is the accuracy with which a drug regimen is initiated and followed [1•]. Compliance includes taking the drug consistently as prescribed by the clinician. One variable often used to measure compliance is the medication possession ratio (MPR) which describes the number of doses available over a fixed period of time—this may be referred to as refill compliance. For example, if a patient purchased an initial (index) prescription and two refills of a 90-day prescription during a single year, the MPR would equal approximately 270/360 or 75%. Persistence is the length of time that a medication is administered correctly. Persistence on a medication often is expressed as the percentage of patients still on medication at a given time with no gap in medication-taking for a period of 30 days or more [2••,3]. Adherence is a combination of compliance and persistence [4].

Measuring Adherence

Studies of compliance, persistence, and adherence are, for the most part, difficult to design and carry out. Measuring medication-taking behaviors without introducing some

Table 1. Overview of compliance rates for chronic diseases

Therapeutic area	Mean compliance rate, %	Range, %
Cancer	80	35–97
Cardiovascular (all)	71	39–93
Hypertension only	73	39–93
Other cardiovascular	71	64–93
Epilepsy	70	46–88
Fertility	71	34–97
Glaucoma	78	76–80
Infectious disease	74	40–92
Medical, general (all)	75	51–85
Diabetes only	73	66–85
Thalassemia only	79	72–85
Other medical only	74	51–84
Medical education	47	–
Psychiatry	78	75–83
Respiratory (all)	54	37–92
Asthma only	55	37–92
Chronic obstructive pulmonary disease only	51	50–52

Adapted from Claxton et al. [7••]

bias can be extraordinarily difficult. Adherence rates measured in clinical trials are likely to be substantially better than those in community outpatient settings [5]. As the focus of the randomized clinical trial design is the efficacy of a pharmaceutical agent, it is essential to have patients adhere to medication routines—in fact adherence is reinforced by study personnel. However, in the community, any attempt to monitor compliance with pharmacotherapy introduces some bias. Data that rely on patient self-reports are potentially inaccurate. A retrospective review of prescription records using pharmaceutical claims or health claims databases also has limitations; filling a prescription is not necessarily the same as taking it. Patients who receive physician office samples are not captured. Records may indicate that an individual has not refilled any prescriptions when actually he or she has switched insurance providers and refills just have not been recorded. Continuous enrollment in the health plan(s) monitored by the database is therefore important. Finally, the definition of "good" adherence is arbitrary and varies across published studies. In a recent article, Osterberg and Blaschke [6••] noted the variability in measures of compliance in clinical trials. For example, some clinical trials accept adherence rates of greater than 80%, while others believe that anything less than 95% adherence is unacceptable. Perhaps "good" adherence should be defined as the threshold below which adverse health consequences occur. However, there are no data to suggest that such a threshold exists; rather adherence and adverse consequences occur on a continuum.

Table 2. Discontinuation rates on osteoporosis medications

Type of therapy	Number initiating medication for osteoporosis	Number discontinuing medication (% of sample)
Hormone replacement therapy	334	88 (26%)
Raloxifene	256	48 (19%)
Alendronate	366	70 (19%)

Data from Tosteson et al. [10•].

Adherence and Chronic Diseases

Patients display poor compliance with pharmaceutical treatments for virtually all chronic illnesses. A study by Claxton et al. [7••] showed that, regardless of therapeutic area, mean compliance rates with all drugs were poor (Table 1). Moreover, compliance rates do not seem to be influenced by the nature or severity of the disease being treated. For example, Claxton et al. [7••] reported that slightly more than 50% of patients with chronic obstructive pulmonary disease were compliant with therapy (range 50%–52%). Among patients with cardiovascular disease, 70% were compliant (range 39%–93%). Even a proportion of cancer patients display poor compliance; only about 80% take their medications as directed (range 35%–97%). Compliance is especially challenging with medications for asymptomatic or silent diseases such as hypertension [8,9] or osteoporosis. These conditions pose a unique problem in that they are not associated with noticeable symptoms or symptom relief and patients may feel that medications are unnecessary.

Adherence with Osteoporosis Medications

Individuals who take medications for osteoporosis display the same degree of non-adherence to therapy as those who take medications for other chronic asymptomatic diseases. Adherence data to osteoporosis medications have been obtained in two ways—through self-report by phone interview or questionnaire and by examination of health claims and pharmaceutical benefit databases.

Tosteson et al. [10•] administered a telephone survey to 956 women who had been diagnosed with osteopenia (bone density T-scores between -1.0 and -2.5) or osteoporosis (T-scores ≤ -2.5). None of the women had been treated for osteoporosis, and all were initiating pharmacotherapy (hormone therapy, raloxifene, or alendronate). Nearly 25% (19% to 26%) of patients abandoned osteoporosis therapy within 7 months, regardless of the medication taken (Table 2). Significantly more respondents taking hormone

therapy discontinued treatment compared with raloxifene users ($P = 0.03$) or alendronate users ($P = 0.02$). More than two thirds of women who terminated therapy reported doing so because of side effects. Factors associated with an increased likelihood of discontinuation included side effects and uncertainty around bone density test results. This finding draws attention to the importance of disease status and beliefs about susceptibility to a disease when discontinuing treatment. However, this study is limited in that the medication adherence is not validated and is only based on self-report.

Hamilton et al. [11] reported poor compliance with risedronate in clinical practice based on self-reported results from a questionnaire administered to patients attending an osteoporosis clinic. A total of 219 patients were studied. Adverse events were reported by 38% of patients and led to discontinuation of therapy in 19% (42/219) of patients. Only 10 of the patients who discontinued therapy contacted the clinic for advice and 16 patients attempted a re-challenge of medication. Among these 16, almost 50% were able to resume therapy. Despite counseling and written instructions, 26% of all patients were not taking risedronate correctly.

The poor adherence seen on self-report has been confirmed using claims databases. McCombs et al. [12••] identified over 58,000 patients (the vast majority of whom were female) from a large health insurance database who had initiated daily or weekly osteoporosis therapy. Persistence rates were less than 25% for all therapies at 1 year. In addition, the mean duration of continuous therapy was low across all medications (Table 3).

Some studies have suggested that complex treatment regimens and dosing regimens such as bisphosphonate therapy will reduce the likelihood that patients will remain adherent to medication [6••,7••]. However, extending dosing intervals may improve convenience and adherence. Bisphosphonates are now available with daily, weekly (alendronate, risedronate), and monthly (ibandronate) dosing regimens. Physicians may intuitively believe that longer dosing intervals will be associated with increased adherence, but only a few studies have examined this issue empirically. Ettinger et al. [13] examined persistence with bisphosphonate use in women over 50 years of age, to test the hypothesis that women taking bisphosphonates with longer intervals between doses would be more persistent. They examined pharmacy claims from a longitudinal database which included approximately 25% of all US retail pharmacies. Data were analyzed for new and continuing bisphosphonate users receiving daily ($n = 33,767$) or weekly ($n = 177,552$) therapy. At 1 year, only 15.7% of new daily users and 31.4% of new weekly users were still on therapy. Among women continuing bisphosphonate treatment, 39.0% of patients taking daily bisphosphonates and 58.5% of weekly users remained on medication at the end of 1 year. All differences between persistence with daily versus weekly therapy were significant ($P < 0.0001$).

Table 3. Mean duration of osteoporosis therapy in 1-year retrospective study*

Type of therapy	Mean duration of therapy
Raloxifene	221 days
Bisphophonates	245 days
Estrogen	262 days
Estrogen and progestin	292 days

*$n = 58,109$
Adapted from McCombs et al. [12••]

Thus, in this study, the highest persistence was associated with patients continuing therapy and following the longer interval dosing regimen.

Using a 45-day gap in medication coverage to define lack of persistence with oral bisphosphonates in a pharmacy database, Boccuzzi et al. [14] reported that only 18% of daily users and 22% of weekly users were persistent with treatment at 12 months. Another study compared compliance rates for postmenopausal women treated with raloxifene with those of women receiving alendronate [15]. Just over 900 postmenopausal women were recruited for this 1-year, multi-site, observational trial carried out in Spain (raloxifene group, $n = 476$; alendronate group, $n = 426$). Compliance was measured using three different instruments—the Morisky-Green test, an Autocompliance test, and the Compliance Questionnaire. Among patients who discontinued therapy prematurely ($n = 188$), a greater percentage were taking alendronate versus raloxifene (26% vs 16%). The majority of these patients (74%; 139/188) discontinued during the first 3 months of the study. Adverse events were cited as the reason for discontinuation in significantly fewer patients in the raloxifene group (4.8% vs 11.0% for alendronate users; $P < 0.001$). Finally, from among a variety of demographic variables tested in a logistic regression model, only treatment arm and type of physician (rheumatologist vs orthopedic surgeon) were related to better treatment compliance.

Adherence to Osteoporosis Medication in Patients with Glucocorticoid-induced Osteoporosis

Curtis et al. [16•] evaluated persistence and adherence to alendronate and risedronate among chronic glucocorticoid users enrolled in a US managed care plan. Persistence was defined as no gap in medication for more than 180 days since the last bisphosphonate prescription. Despite adjustment for channeling (preferential prescribing of one medication over the other for patients at risk for gastrointestinal adverse events), no differences in adherence or persistence were noted between the two bisphosphonates. At 2 years, greater than 50% of new users had discontinued bisphosphonate treatment.

Factors associated with discontinuing therapy included advancing age, longer duration of bisphosphonate treatment, bone mineral density (BMD) test findings, and a number of comorbidities [17••,18].

Consequences of Poor Adherence to Medications

Medication non-adherence is the most significant reason for failed pharmacotherapy [19]. Consequences of non-adherence can range from inconsequential to disastrous, depending on drug characteristics, disease state, and severity (eg, drug-resistant strains in human immunodeficiency virus). Asthma patients who are hospitalized or frequently use emergency rooms are more likely to be nonadherent to their medications [20]. In a cohort of elderly patients (mean age = 76.6 years) it was estimated that 11.4% of drug-related hospital admissions were due to medication noncompliance. Further, approximately one-quarter of total hospital costs for drug-related admissions were linked to noncompliance [21•]. Characteristics associated with increased risk for noncompliance-related hospital admissions in this study of the elderly included female gender, poor recall of current medication regimen, being treated by multiple physicians, and median income. Of interest, when a broader definition of noncompliance-related hospital admissions was used, Col et al. [21•] noted that patient's opinions concerning the costs of medications became a significant predictor. A non-significant relationship was also detected between educational level (no high school diploma) and the risk for a noncompliant admission

Consequences of Poor Adherence to Osteoporosis Medications

Poor adherence to osteoporosis medications has been associated with reduced effects on BMD changes, less suppression of bone turnover markers, and increased fractures. Yood et al. [22•] evaluated a cohort of women initiating treatment for osteoporosis following BMD testing. Compliance was defined as the percent of time that patient's refilled their prescriptions and BMD values were obtained at study end (mean follow-up 590 days). Among participants with refill compliance ≥ 66%, mean increases in spine BMD were 3.8% per year, versus patients with refill compliance ≤ 66%, who reported mean increases in BMD of 2.1% per year. Similar findings were reported by Clowes et al. [23•] who studied the impact of nurse- and marker-monitoring (urinary N-telopeptide of type I collagen or uNTX, a marker of bone resorption) on adherence to osteoporosis medications and treatment efficacy. In this study, cumulative adherence was calculated as number of tablets taken/number of tablets prescribed since randomization, using an electronic monitoring device. Adherence to therapy at 1 year was positively correlated to percent changes in hip BMD ($P = 0.01$; but not lumbar spine BMD) and suppression of uNTX ($P = 0.002$) from baseline. A study of fracture risk and compliance with osteoporosis medications was completed by Caro et al. [24••] using health data files from over 11,000 women in Saskatchewan. Compliance was defined as an MPR of 0.80 (drug available 80% of the time). Compliant patients experienced a 16% lower fracture rate compared with noncompliant patients (hazard ratio = 0.81; $P = 0.0009$). These researchers identified age greater than 75 years, short term history of fracture, and prior use of osteoporosis medications or steroids to be independent predictors of increased fracture risk.

A retrospective analysis of claims from two large pharmaceutical databases covering over 6 million lives evaluated risk for specific fracture types in women initiating bisphosphonate treatment for postmenopausal osteoporosis [25••]. Over 35,000 women aged 45 years or older initiated bisphosphonate therapy; of these, 43% were refill compliant (MPR ≥ .80) and 20% persisted with treatment after two years. Women who achieved compliance with therapy had a 21% reduction in fractures overall compared with those who were not compliant. The adjusted relative risk for all nonvertebral fractures was 20% lower in women who were refill-compliant than in those who were not ($P < .0001$) and when hip fractures were analyzed separately, the adjusted risk was 37% lower for compliant women ($P < .0001$ vs noncompliant women). Wrist fractures were less common in compliant women but this difference was not statistically significant.

McCombs et al. [12••] also found that good compliance with therapy was associated with positive health outcomes. Compliance in this database analysis reduced the risk for hip fracture (OR = 0.382; $P < 0.01$) and vertebral fracture (OR = 0.601; $P < 0.05$). Further, compliant patients used fewer physician services (-US $56; $P < 0.0001$), fewer hospital outpatient services (-US $38; $P < 0.05$), and less hospital care (-US $155, $P < 0.01$). These findings provide evidence that non-compliant patients may be at higher risk for fracture and excessive health care costs.

Barriers to Adherence to Medication

Knowing the adverse consequences of poor adherence, what are the individual and cultural barriers contributing to poor medication adherence? The list is long and, of course, varies by disease and patient population. Certainly the presence of psychiatric conditions, particularly depression, can impede adherence to medication regimens. In addition, cognitive impairment or dementia has a negative effect on adherence. Asymptomatic diseases, negative side effects, and complexity of treatment regimens impact adherence. Finally, inadequate follow-up on the part of the physician or other health care professional or poor discharge planning can lead to poor adherence rates [6••].

Additional barriers to adherence include the patient's disbelief that treatment will be beneficial. Patients who lack insight into their illness and into the consequences of their illness and the consequences of poor adherence to medication regimens will also be less likely to take their medications as indicated, particularly over long periods of time. Poor physician-patient relationships are associated with reduced adherence, as are higher costs of medications and co-payment expectations. Finally, missed office appointments can be a sign of poor adherence and should be followed-up [6••]. Several recent studies that have focused on discrete factors influencing medication adherence are described below.

Factors That Predict Adherence to Osteoporosis Therapy

Information on patients initiating medication to treat osteoporosis was gathered from tertiary care centers in Canada by Papaioannou et al. [17••]. In this observational study, non-adherence was defined as simple discontinuation at any time. A Cox proportional hazards model was used to examine differences across treatment groups (etidronate, alendronate, or hormone therapy) in time to discontinuation. Among patients receiving any medication, 70% were persistent with therapy at 3 years. The Cox model demonstrated that alendronate treated patients were 40% more likely to discontinue treatment compared with etidronate treated patients. Two additional independent predictors of greater persistence with therapy included the presence of incident vertebral fractures (HR = 0.424) and older age (HR = 0.985). Determinants of compliance were analyzed by Solomon et al. [18] using a pharmacy claims database to track patients older than 65 years of age initiating pharmacotherapy for osteoporosis. Compliance was defined as medication available ≥ 66% of the time for a 60-day period. Over 45% of patients were no longer refill compliant at the end of 1 year and 52% had stopped filling prescriptions at the end of 5 years. Characteristics that predicted compliance were female gender, younger age, fewer comorbid conditions, fewer medications, BMD testing, history of previous fracture, and nursing home residency.

Adherence with Osteoporosis Medications: Why So Poor?

An informal review of the literature reveals a variety of factors that may be directly or indirectly involved in poor adherence to osteoporosis medications; these include:

- Inadequate information about the disease.
- Inadequate health care provider-patient interaction.
- The asymptomatic nature of osteoporosis.
- Need for chronic treatment.
- Drug-associated adverse effects.
- Personal beliefs and fears.
- Differences in perspectives between physicians and patients.
- Problems associated with treating an elderly population.

Pickney and Arnason [26] suggested that inadequate patient education about osteoporosis and DXA results have contributed to poor medication adherence. Using data from over 1000 residents of rural Wisconsin following BMD testing, these investigators found that a wide gap existed between the participants' understanding of their T scores and the actual scores and associated diagnoses. For example, only 63% of those with normal BMD correctly recalled this and only 31% of those with osteopenia and 50% of patients with osteoporosis correctly reported these results. Patients with low BMD who correctly reported the results of their BMD test were significantly more likely to continue taking their osteoporosis medication. This finding emphasizes the critical nature of good communication between provider and patient as well as the importance of accurate disease-related information. Correct understanding of DXA information may lead to improved adherence in patients with low BMD.

Osteoporosis patients are often elderly. The elderly frequently have concurrent illnesses and conditions requiring multiple medications, along with some degree of cognitive decline and forgetfulness. Roth and Ivey [27•] evaluated 100 elderly patients in the community who took an average of 9.6 medications. Data on self-reported nonadherence was high at 53%. Nonadherence was related to race, health literacy, and functional capacity.

Strategies for Improving Adherence to Osteoporosis Medications

A variety of strategies to encourage better adherence to osteoporosis therapies have been proposed, and some have been the subject of research studies. One strategy may be the use of medications with extended dosing intervals. The development of medications, such as oral bisphosphonates administered once-monthly (ibandronate), intravenous bisphosphonates administered every 3 months (ibandronate), or intravenous agents given twice yearly (denosumab), or infused once yearly (zolendronate) may provide an opportunity to improve adherence. However, the use of medications with extended dosing intervals may also increase the likelihood of forgetting medications, an omission associated with greater clinical consequences. In this regard, the use of patient reminder programs may be extremely important for reinforcing treatment adherence. While many anticipate improvements in adherence with the newly approved monthly oral bisphosphonate, data from medical claims databases will be needed to support this assumption and evaluate the size of the effect. What remains unclear is whether

a maximum threshold for improving adherence with extended dosing intervals will be reached and at what point adherence behavior may become dependent upon other factors such as physician-patient communication or cognitive function.

Several studies have attempted to use bone turnover marker findings to improve compliance. Nattras et al. [28] evaluated 280 patients randomized to four study arms characterized by the type of information provided to patients as follows: uNTx levels at 3 months, patient education, uNTx levels and patient education, and no intervention. After 12 months no differences were seen in the number of months on therapy across these distinct intervention cohorts. In the study by Clowes et al. [23•], nurse monitoring was associated with an increase in cumulative adherence to osteoporosis therapy of 57% at 1 year versus no monitoring. Monitoring based on bone turnover molecules did not improve adherence or persistence when compared with nurse monitoring alone. Finally, the Improving Measurements of Persistence with Actonel Therapy study (IMPACT) was a 1-year, multicenter study of 2302 postmenopausal women with osteoporosis aged 65 to 80 years [29]. Centers were randomized into reinforcement (Re+) or non-reinforcement (Re-) groups. The Re+ groups received bone turnover markers (BTM) information at weeks 10 and 22 with positive messaging. A 13% reduction in the hazard of discontinuation in the Re+ group versus the Re- group was seen (HR = 0.87; $P = 0.16$). The overall persistence rates as measured by an electronic sensing device in the medication bottle at 1 year were surprisingly high for both study groups (Re+ = 79.8% and Re- = 77.2%). In this study, significant improvements in persistence with therapy were achieved through BTM reinforcement in patients with no osteoporosis risk factors at baseline. Alternative monitoring mechanisms should be created as part of clinical efforts to improve adherence to osteoporosis medications. The development of point-of-service markers or automated bone marker monitoring may enable clinicians to identify individuals with poor adherence easily.

To impact adherence, physicians must form a partnership with their patients. Communication and trust between the physician and patient are crucial. The patient must understand the problems presented by impending bone loss and appreciate his or her personal involvement in the solution. Information exchange should occur at the point of service. The physician must interact effectively with patients and make accommodations for their life styles and needs as part of choosing the optimal osteoporosis therapy.

Conclusions

Adherence to therapy for postmenopausal- or glucocorticoid-induced osteoporosis remains poor and may be associated with long-term consequences such as increased osteoporotic fractures, including nonvertebral and hip fractures. Intermediate endpoints, such as insufficient changes in BMD and lesser suppression of bone markers provide surrogates for possible noncompliance. Potential solutions include newer medications with extended dosing intervals, monitoring, and enhanced physician-patient relationships.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.• Sclar DA, Chin A, Skaer TL, et al.: **Effect of health education in promoting prescription refill compliance among patients with hypertension.** *Clin Ther* 1991, **13:**489–495.
Health education may improve adherence.

2.•• Cramer JA, Amonkar MM, Hebborn A, Altman R: **Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis.** *Curr Med Res Opin* 2005, **21:**1453–1460.
Adherence is improved with weekly versus daily bisphosphonates.

3. Sikka R, Xia F, Aubert RE: **Estimating medication persistency using administrative claims data.** *Am J Manag Care* 2005, **11:**449–457.

4. Dezii CM: **Persistence with drug therapy: a practical approach using administrative claims data.** *Manag Care* 2001, **10:**42–45.

5. Hart JT: **Commentary: can health outputs of routine practice approach those of clinical trials?** *Int J Epidemiol* 2001, **30:**1263–1267.

6.•• Osterberg L, Blaschke T: **Adherence to medication.** *N Engl J Med* 2005, **353:**487–497.
An excellent review of the problem of poor adherence with all therapies.

7.•• Claxton AJ, Cramer J, Pierce C: **A systematic review of the associations between dose regimens and medication compliance.** *Clin Ther* 2001, **23:**1296–1310.
Another excellent review of the relationship between dosing and compliance.

8. Berg JS, Dischler J, Wagner DJ, et al.: **Medication compliance: a healthcare problem.** *Ann Pharmacother* 1993, **27(Suppl 9):**S1–S24.

9. Miller NH: **Compliance with treatment regimens in chronic asymptomatic diseases.** *Am J Med* 1997, **102:**43–49.

10.• Tosteson AN, Grove MR, Hammond CS, et al.: **Early discontinuation of treatment for osteoporosis.** *Am J Med* 2003, **115:**209–216.
An early article on poor adherence using telephone survey.

11. Hamilton B, McCoy K, Taggart H: **Tolerability and compliance with risedronate in clinical practice.** *Osteoporos Int* 2003, **14:**259–262.

12.•• McCombs JS, Thiebaud P, McLaughlin-Miley C, Shi J: **Compliance with drug therapies for the treatment and prevention of osteoporosis.** *Maturitas* 2004, **48:**271–287.
A large review of insurance claims data showing poor adherence with bisphosphonate therapy.

13. Ettinger M, Gallagher R, Amonkar M, et al.: **Medication persistence is improved with less frequent dosing of bisphosphonates, but remains inadequate [abstract].** *Arthritis Rheum* 2004, **50(Suppl 1):**S513–S514.

14. Boccuzzi SF, Omar SH, Kahler MA: **Assessment of adherence and persistence with daily and weekly dosing regimens of oral bisphosphonates.** *Paper Presented at the 5th European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis.* Rome, Italy; March 2005.

15. Turbi C, Herrero-Beaumont G, Acebes JC, et al.: **Compliance and satisfaction with raloxifene versus alendronate for the treatment of postmenopausal osteoporosis in clinical practice: an open-label, prospective, nonrandomized, observational study.** *Clin Ther* 2004, **26:**245–256.

16.• Curtis JR, Westfall AO, Allison JJ, et al.: **Persistence and adherence to alendronate and risedronate among chronic glucocorticoid users [abstract].** *Arthritis Rheum* 2005, **52(Suppl 9):**s374.

This abstract is the first to show that patients at high risk for fracture on glucocorticoids have similar problems with adherence.

17.•• Papaioannou A, Ioannidis G, Adachi JD, et al.: **Adherence to bisphosphonates and hormone replacement therapy in a tertiary care setting of patients in the CANDOO database.** *Osteoporos Int* 2003, **14:**808–813.

This paper showed decreased BMD response and a trend toward greater 10 year fracture risk in nonadherent patients using a national database of tertiary specialists.

18. Solomon DH, Avorn J, Katz JN, et al.: **Compliance with osteoporosis medications.** *Arch Intern Med* 2005, **165:**2414–2419.

19. O'Brien MK, Petrie K, Raeburn J: **Adherence to medication regimens: updating a complex medical issue.** *Med Care Rev* 1992, **49:**435–454.

20. Bender B, Milgrom H, Rand C: **Nonadherence in asthmatic patients: is there a solution to the problem?** *Ann Allergy Asthma Immunol* 1997, **79:**177–186.

21.• Col N, Fanale JE, Kronholm P: **The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly.** *Arch Intern Med* 1990, **150:**841–845.

Poor adherence results in increased hospitalizations

22.• Yood RA, Emani S, Reed JI, et al.: **Compliance with pharmacologic therapy for osteoporosis.** *Osteoporos Int* 2003, **14:**965–968.

This paper showed the adverse consequences of poor adherence on BMD.

23.• Clowes JA, Peel NF, Eastell R: **The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial.** *J Clin Endocrinol Metab* 2004, **89:**1117–1123.

Monitoring with biochemical markers did not improve compliance but increased health care provider interaction did.

24.•• Caro JJ, Ishak KJ, Huybrechts KF, et al.: **The impact of compliance with osteoporosis therapy on fracture rates in actual practice.** *Osteoporos Int* 2004, **15:**1003–1008.

This paper was one of the first to show the adverse consequences of poor adherence on fracture rate.

25.•• Siris E, Harris ST, Rosen CJ, et al.: **Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and non-vertebral fractures from a US claims database.** *JAMA* 2006, In press

This paper shows us the adverse consequences of poor adherence in terms of increased nonvertebral fracture rates.

26. Pickney CS, Arnason JA: **Correlation between patient recall of bone densitometry results and subsequent treatment adherence.** *Osteoporos Int* 2005, **16:**1156–1160.

27.• Roth MT, Ivey JL: **Self reported medication use in community residing older adults: a pilot study.** *Am J Geriat Pharmacother* 2005, **3:**196–204.

This paper discusses the polypharmacy seen in elderly adults

28. Nattras S, Silverman S, Drinkwater B: **Effectiveness of education and/or NTx results as a means of encouraging compliance to alendronate.** *Presented at the World Congress on Osteoporosis*. Chicago, IL; May 2000.

29. Delmas PD, Vrijens B, Roux C, et al.: **Reinforcement Message Based on Bone Turnover Marker Response Influences Long-Term Persistence with Risedronate in Osteoporosis: The IMPACT Study Abstract M330.** *Presented at the meeting of the American Society of Bone and Mineral Research*. Minneapolis, MN, September 2003.