Adherence to Medications for the Treatment of Osteoporosis

a report by

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We are fortunate to have therapies for osteoporosis with proven efficacy in randomized clinical trials. Unfortunately, the efficacy of these therapies is often limited by poor adherence.

Osteoporosis for most of our patients is a chronic asymptomatic illness which only becomes symptomatic with fracture. Like other asymptomatic illnesses, adherence is often poor because our patients do not see changes in symptoms that they can recognize. Improvements are measured by changes in BMD which may take years.

This article discusses rates of adherence to osteoporosis therapies, and reasons underlying poor adherence. The article concludes by reviewing strategies to improve adherence.

Definitions

In order to understand the literature on adherence to osteoporosis medications, we need to understand three words which are often used interchangeably despite differences in meanings: compliance, persistence, and adherence. I refer the reader to the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) definitions: Medication Compliance is the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen. The unit of measure for compliance is the number of doses available to the patient during a specific time interval (this has sometimes been called refill compliance). For example, if your patient takes a medication assuming no large refill gaps, persistence is the length of time that a patient takes a medication assuming no large refill gaps. Persistence on a medication may be expressed as the percentage of patients still on medication at a given time such as 12 months with no gap in medication-taking for a period of 30 days or more. Adherence has also been used as a global term which encompasses both compliance and persistence. This definition will be used in this review.

Measuring Adherence

Available data on adherence is derived from three methods: clinical trials, telephonic or mail survey, and medical claims databases. Each method has its own limitations. Subjects in clinical trials often have better adherence than patients in the community. Patients interviewed by telephone or by mail survey may overstate their adherence to please the interviewer or are embarrassed to admit poor adherence. Medical claims databases while more ‘real world’ are also limited. Prescription samples in the physician office are not captured. Patients who change insurance plans to an insurance plan not in the database may not be captured and may be thought to have discontinued medications. An important inclusion criteria may be continuous enrollment in the health plan during period of study. Changes in a preferred drug based on contractual changes may occur during the period of observation as well.

Adherence with Osteoporosis Medications

Patients with osteoporosis, like other patients with chronic asymptomatic illnesses, are often uncompliant with their medication. Using a telephone survey, Tosteson interviewed 956 women with osteopenia or osteoporosis who had been started on therapy. Nearly one-quarter (19% to 26%) of patients abandoned osteoporosis therapy (including both hormone replacement therapy (HRT) and bisphosphonates) within seven months. Women who discontinued were
more likely to do so because of side effects or uncertainty about the severity of their illness based on their bone density results. However, this study is limited in that it is based on self-report and as noted above telephone surveys may overestimate adherence.

Hamilton et al. reported poor compliance with risedronate in clinical practice based on self-reported results from a questionnaire. A total of 219 patients were studied. Despite counseling by the healthcare provider and written instructions, 26% of all patients were not taking their osteoporosis medication correctly.

Medical claims databases have also confirmed that osteoporosis patients have poor adherence to their therapies. McCombs looked at 58,000 patients (mostly female) in a large health insurance database who had started daily or weekly osteoporosis therapy. Persistence rates at 12 months were less than 25% for all therapies.

Ettinger and colleagues examined persistence with daily and weekly bisphosphonate therapy in women over 50 years of age by examining pharmacy claims from a longitudinal database which included approximately 25% of all US retail pharmacies. Data were analyzed for both new and continuing bisphosphonate users receiving either daily (n=33,767) or weekly (n=177,552) therapy. At one year, only 15.7% of new daily users and 31.4% of new weekly users were still on therapy. Among women with prior bisphosphonate use, 39.0% of patients taking daily bisphosphonates and 58.5% of weekly users remained on medication at the end of one year (p < 0.0001).

Bocuzzi reported that only 18% of daily users and 22% of weekly users were persistent with treatment at 12 months in a pharmacy claims database with a definition of persistence being no gap greater than 45 days.

Cramer studied 12 month persistence using an administrative claims database in 2,741 women who were prescribed a daily or weekly bisphosphonate. Persistence was 44.2% for women taking a weekly bisphosphonate and 31.7% for women taking a daily bisphosphonate. Recker using a retail pharmacy database found that only 25.2% of weekly and 13.2% of daily bisphosphonate users had adequate amount of medication as defined by a medication possession ratio of greater than 80%.

Blouin, using an administrative database in Quebec found that 12 month medication compliance was significantly higher in elderly women (greater than 70 years) who are started on osteoporosis therapy for secondary prevention than those who are started for primary prevention (61% vs 55%, p<0.01). Secondary prevention was defined as an ICD-9 code for osteoporosis or fracture. Women using the greatest number of pharmacies and physicians had lower compliance while women who had BMD testing or had a fracture had better compliance.

Nichol studied discontinuation and restart behavior with risedronate and alendronate in a large western US physician group with access to integrated administrative data. Approximately 37% of both the alendronate and risedronate users who discontinued therapy for at least 90 days restarted therapy at some time in the study year. Of the women who discontinued therapy for more than 90 days, risedronate initiators averaged 174 days to restart therapy, while alendronate users averaged 154 days (p=0.059). Risedronate users were more likely to maintain therapy without 15 day gaps more consistently (p=0.021). Van den Boogaard consistent with Nichol’s data found that about 30% of nonpersistent bisphosphonate users resumed treatment in the first year using an integrated claims database in The Netherlands.

**Consequences of Poor Adherence to Osteoporosis Medications**

Poor adherence to osteoporosis medications has been associated with less improvement in bone mineral density (BMD), less suppression of bone turnover markers, and increased risk of fractures. Yood et al. studied the relationship between compliance to osteoporosis medication and changes in BMD in patients initiating therapy. 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. Clowes et al. studied the relationship between adherence and both BMD and bone turnover markers (urinary N-telopeptide of type I collagen or uNTX, a marker of bone resorption) on. 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 one 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 more important consequence of poor adherence is increased fracture risk. Caro et al. studied the relationship between adherence and fracture risk using a claims database of 11,000 women in Saskatchewan. Compliance was defined as an MPR of .80 (drug available 80% of the time). Compliant patients
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experienced a 16% lower fracture rate compared to noncompliant patients (hazard ratio=0.81; p=0.0009).

Siris and colleagues did a retrospective study of the relationship between adherence to bisphosphonate therapy and the risk of vertebral and nonvertebral fractures, during a five-year period (1/1/99-12/31/2003) using two large pharmaceutical databases in six million individuals. The eligible cohort included 35,537 women ≥45 years of age, prescribed a bisphosphonate with data available for a 24 month period after the index prescription. Persistence was defined as no gap in refills ≥30 days over 24 months, and refill compliance was defined as a medication possession ratio of ≥80%. A total of 43% of women were refill compliant and 20% were persistent with bisphosphonate therapy over the 24 month study period. Relative risk reductions of 37% and 40% vertebral fractures and 20% and 29% for nonvertebral fractures were observed in the compliant (vs non-compliant) and persistent (vs non-persistent) cohorts respectively. Adjustment for baseline factors did not affect the significance of the relationship. There was a relationship between refill compliance and fracture risk reduction which was first evident at refill compliance rates around 50% but became progressively more robust as compliance increased.

McCombs also using a large medical claims database found that good compliance with therapy was associated with decreased fracture risk and decreased healthcare costs. Compliance in this database analysis reduced the costs. Compliance in this database analysis reduced the

In a recent survey, over half of (51%) of women prescribed osteoporosis medication did not recall how long they were to stay on their osteoporosis medication. A few women believed they needed only to remain on therapy for six months or until their present course was finished. In this same survey, disturbingly 27% of women thought that their risk of fracture was the same regardless of whether or not they took their osteoporosis medication. Twenty percent were unaware of treatment benefits and 17% did not believe that their treatment had any benefit at all. Side effects and restrictions on how to take medications were the main drawbacks associated with treatment by the women in the survey, with staying upright as the biggest inconvenience associated with bisphosphonate therapy.

Osteoporosis patients are often elderly. The elderly frequently have concurrent illnesses and conditions requiring multiple medications, along with some degree of memory loss. Roth evaluated 100 elderly patients in the community who took an average of 9.6 medications. non-adherence was high at 53%.

Two recent studies have looked at factors influencing adherence. Papaioannou in Canada found that two factors: prevalent vertebral fracture and older age predicted better adherence. Solomon using a managed care claims database found that female gender, younger age, multiple medications, multiple comorbid conditions, prevalent fracture and nursing home residency also predicted adherence.

**Barriers to Adherence to Osteoporosis Medication**

The health belief model may be helpful in understanding barriers to adherence to osteoporosis medications. Patients who do not believe that they have osteoporosis and who do not understand the consequences of osteoporosis will be less likely to take their medications. Similarly, patients who do not believe that treatment will be beneficial will be less likely to be adherent.

Our patients may not understand their diagnosis of osteoporosis or their medication. Pickney and Arnason studied the relationship between understanding of DXA results and adherence. The investigators queried 1,000 residents of rural Wisconsin who had had a DXA test. Only 63% of those with normal BMD correctly recalled this and only 31% of those with osteopenia and 50% of patients with osteoporosis correctly remembered their results. Patients who had had a low BMD and who remembered their results as being low were significantly more likely to continue taking their osteoporosis medication. This finding emphasizes the importance of good communication with our patients and patient understanding of their diagnosis. Correct understanding of DXA information may lead to improved adherence in patients with low BMD.

Cochrane review in 2005 found that less than half of interventions which have been tested in randomized trials improved adherence and less than one-third improved outcomes Effective interventions were
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usually complex, involving combinations of several interventions not simply one intervention. Unfortunately, even effective interventions did not have sustained benefits beyond six months. Integrating patient preferences into treatment plans may be the most practical way to improve adherence.

One strategy may be to use osteoporosis medications with extended dosing intervals. The development of medications, such as oral bisphosphonates administered once-monthly (ibandronate), intravenous bisphosphonates administered every three months (ibandronate), or agents injected subcutaneously twice yearly (denosumab), or infused once yearly (zolendronate) may provide an opportunity to improve adherence above current levels. However, the use of medications with extended dosing intervals may also increase the likelihood of forgetting medications with associated greater clinical consequences.

The use of patient support programs may be extremely important for reinforcing treatment adherence, especially with extended dosing intervals. Patient support programs may use telephone, ordinary mail or email. Cooper reported the success of patient support programs may use telephone, ordinary mail or email. Persistence between these two cohorts were persistently compared to a weekly bisphosphonate. Programs plus monthly ibandronate in improving support programs may use telephone, ordinary mail or email. Cooper reported the success of patient support programs may use telephone, ordinary mail or email. Especially with extended dosing intervals. Patient support programs may use telephone, ordinary mail or email. Important for reinforcing treatment adherence, the use of patient support programs may be extremely important for reinforcing treatment adherence. The development of medications, such as oral bisphosphonates administered once-monthly (ibandronate), intravenous bisphosphonates administered every three months (ibandronate), or agents injected subcutaneously twice yearly (denosumab), or infused once yearly (zolendronate) may provide an opportunity to improve adherence above current levels. However, the use of medications with extended dosing intervals may also increase the likelihood of forgetting medications with associated greater clinical consequences.

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Confirmation that extended dosing intervals approve adherence will rely on data from medical claims databases. What is not known is whether there is a maximum adherence we can achieve by simply extending dosing intervals alone.

We have assumed that giving feedback to patients would improve adherence. Such information could be bone marker or BMD information. Since the majority of patients may stop their osteoporosis medication prior to one or two years when we do a bone density, there has been interest in studying the impact of bone density information. In a study by Clowes et al., patients monitored by a nurse had greater adherence to osteoporosis therapy than those who received no monitoring. Patients who met with a nurse had equivalent adherence to those who met with a nurse and received bone marker information. In a third study on bone marker information, 2,302 post-menopausal women with osteoporosis aged 65–80 years were studied in a one-year multicenter study. Persistence was measured by an electronic sensing device in the medication bottle. Centers were randomized into reinforcement groups who received bone marker information at weeks 10 and 22 and nonreinforcement groups who did not receive bone marker information. There was 13\% less persistence in the nonreinforcement group (HR=0.87; \( p=0.16 \)). However, the overall persistence rates were surprisingly high for both study groups (79.8\% and 77.2\%). These three studies therefore, did not show significant effects of bone marker information as feedback to improve adherence.

In order for us as healthcare providers to improve adherence to osteoporosis medication, we need to improve our communication with patients. Our patients need to understand that they have osteoporosis, that their osteoporosis is associated with significant negative consequences such as fracture. Our patients need to understand that there are effective medications which can reduce their risk of fracture. As healthcare providers we need to talk with our patients about both the efficacy and side effects of medications. We need to talk in terms of emphasizing how fractures will impact that patients valued priorities, such as caring for grandchildren. We need to find out if there are barriers to taking medications and discuss with our patients how to resolve these barriers. We should consider finding out our patients’ preferences for dosing interval: daily, weekly or monthly or intravenously every three months. Conclusions

Adherence to osteoporosis therapies for post-menopausal osteoporosis remains poor and is associated with long-term consequences such as increased osteoporotic fractures, including non-vertebral and hip fractures. Potential solutions include newer medications with extended dosing intervals, monitoring, patient support programs and improved communication between healthcare providers and patients. A version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchbriefings.com).