

## Therapeutic Adherence with Bisphosphonates in the Treatment of Osteoporosis

a report by

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The single most important public health problem facing physicians today may be the failure of patients to follow their prescribed treatment regimens, a phenomenon that results in treatment failures, increased morbidity and mortality and enormous burdens to society and the economy. As is the case with many chronic diseases, the problem of adherence to therapy has emerged as a significant challenge to the successful management of osteoporosis. Despite the availability of effective, well-tolerated drugs for osteoporosis, fracture rates remain high, due in part to poor compliance and persistence with medication.

### Adherence to Current Bisphosphonate Therapy

Bisphosphonates are usually the first-line treatment option for post-menopausal osteoporosis because of their ability to provide substantial increases in bone mineral density (BMD) at the lumbar spine and hip, and to significantly decrease bone turnover, which translates into reductions in the risk of vertebral fractures of up to 65% and of non-vertebral fractures of up to 53%. However, long-term adherence to therapy is required for optimal therapeutic benefit for patients with osteoporosis.

An open-label, observational, clinic-based study of daily oral alendronate, the most prescribed bisphosphonate, in post-menopausal women with osteoporosis or osteopenia investigated persistence. Of the 401 patients recruited, 13% did not even start therapy, and of those who did start, the probability of persisting with therapy was 49% at 12 months and 30% at 24 months. Similar findings were reported in another study of more than 1,800 patients with osteoporosis. In this study, a fifth of patients stopped treatment in the first four months.

In the Canadian Database of Osteoporosis and Osteopenia (CANDOO), persistence with current bisphosphonates decreases over time, with 29.9% and 35.8% of 477 patients discontinuing treatment with daily alendronate after one and two years of treatment, respectively. Ettinger et al. reported that

the rate of discontinuation of alendronate treatment increased linearly over time, with almost half of the women followed (46.1%) having discontinued therapy by the end of 10 months of follow-up.

Although the introduction of weekly formulations improved adherence compared with daily regimens, levels still remain suboptimal.

The results of a US-based observational study showed that treatment adherence was significantly greater in patients receiving once-weekly bisphosphonates than in those receiving daily therapy over one year. A total of 2,741 women were identified from administrative claims data. Patients had been provided with a new prescription for daily or weekly oral bisphosphonate. Compliance, as assessed by mean medication possession ratio (MPR), defined as the number of days the drug was supplied divided by the number of follow-up days, was significantly higher in patients receiving once-weekly bisphosphonates than in those receiving daily treatment (69.2% versus 57.6%;  $p < 0.0001$ ). At the end of the 12 months, more women receiving once-weekly bisphosphonates persisted with therapy than those receiving daily regimens (44.2% versus 31.7%), but the rates of persistence were suboptimal in both dosing regimens.

An analysis of prescriptions from 25% of US retail pharmacies, recorded on a longitudinal patient database performed in 211,319 patients receiving daily or weekly bisphosphonates, showed that adequate compliance (defined as  $MPR > 80\%$ ) was significantly higher in patients receiving weekly therapy compared to those receiving daily therapy. Over the year of follow-up, the worst adherence was observed for patients new to bisphosphonates (13.2% for daily and 25.2% for weekly regimens).

Van Staa et al. examined two databases containing medical records of medical practitioners in the UK and identified 12,373 patients initiated on either alendronate or risedronate treatment. The one-year persistence was 68.7% with weekly and 57.5% with daily regimens.



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### Impact of Suboptimal Adherence to Bisphosphonates on Clinical and Economic Outcomes

Regular use of bisphosphonate therapy is important to prevent fractures and chronic disability. Indeed, inadequate use of bisphosphonates leads to inadequate reduction of biochemical markers of bone turnover, insufficient increases in BMD and increased fracture risk.

A subanalysis of the IMPACT study database, including 2,302 osteoporotic women, showed that a clinically significant decrease (>50%) in the biochemical marker of bone resorption was found in more than 60% of patients who take their risedronate treatment consistently, compared with only 20% of poorly compliant patients. The relationship between suboptimal use of bisphosphonates and adverse impact on BMD has been demonstrated in several studies. In a study including 176 new users of bisphosphonates, it was found that patients who took at least two-thirds of their bisphosphonate medication showed significantly higher increases in BMD at the lumbar spine (3.8%) and hip (2.6%), than patients who were less compliant (2.1% and 2.3%, respectively;  $p < 0.006$ ). Similar findings from a questionnaire that included 240 patients showed that compliant patients achieved BMD gains of 4.3% and 1.2% at the lumbar spine and hip, while women taking less medication demonstrated modest gains of only 2.8% and 0.3%, respectively. In the CANDOO study, a statistically significant difference was observed between consistent and inconsistent bisphosphonate users for increases in lumbar spine BMD after one, two and three years. The consistent users group had significant increases in BMD during each year of the study, whereas there were no significant increases in BMD for the inconsistent user group until year three, when a modest gain of 3.2% was recorded.

Many studies have also demonstrated that patients who do not take adequate amounts of bisphosphonate are at greater risk of fracture. In an analysis of a US claims database, it was demonstrated that the likelihood of fracture was reduced if compliance was maintained for one year, compared with patients switching or discontinuing therapy. Adherent patients had a significantly lower risk of fractures at the spine (odds ratio (OR)=0.6;  $p < 0.05$ ) and hip (OR=0.38;  $p < 0.01$ ), compared to non-adherent patients. Similar findings from a Canadian database that included 11,249 women showed that highly compliant patients (MPR>80%) had a 16% lower fracture rate (hazard ratio=0.84;  $p < 0.005$ ) than low compliant patients. In the CANDOO study, there was a non-significant trend towards a 27% greater 10-year fracture risk among patients taking therapy inconsistently.

Most importantly, Siris et al. estimated the probability of fracture along a gradient of adherence. This retrospective study used two large pharmaceutical databases. The overall fracture rate was 29% lower for women without a refill gap than for those who were not persistent with therapy. At an MPR from 0% to 50%, the probability of fracture during a period of 24 months remained consistent at about 11%. These results are supported by Huybrechts et al. In this study, relative risk of fracture in patients with 80–90% 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%. Eventually, there is a significant association between poor compliance and economic outcomes. McCombs, using a large medical claims database, found that good compliance with therapy was associated with decreased fracture risk and decreased healthcare costs.

### Factors Affecting Adherence to Bisphosphonate Treatment

Although bisphosphonates improve the outcomes of osteoporosis, many patients are reluctant to take them. A major reason is because osteoporosis is an asymptomatic, chronic condition. This difficulty is compounded further by the fact that, in asymptomatic condition, the benefits of treatment are not immediately apparent and, consequently, patients do not consider themselves in need of medication.

Patients with concurrent illnesses and conditions requiring multiple medications may be at a greater risk of discontinuing with therapy. In a recent study conducted by Curtis et al., it was shown that an increased burden of medical comorbidity decreased the likelihood to persist with therapy. The authors also demonstrated that younger age and lack of BMD testing were associated with discontinuation.

Adherence to medications is complicated by the lack of options for patients' self-monitoring. Measurement of BMD or biochemical markers of bone turnover could be used by physicians to provide feedback to patients on the effectiveness of medication, but feedback systems are costly and not readily available. An additional barrier to treatment adherence is that current oral bisphosphonates need to be administered according to strict treatment guidelines, including remaining upright and not eating, drinking or taking other medications for up to 60 minutes after the bisphosphonate intake. These complex dosing instructions are necessary to maximise the bioavailability of bisphosphonates and reduce the risk of adverse events. However, these requirements can be inconvenient for patients,

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especially those taking daily therapy, and may reduce compliance. The impact of failure to follow dosing guidelines is illustrated in a study of 219 women receiving alendronate. Despite receiving counselling and written instructions, almost 26% of women were not compliant with instructions.

Tolerability is another factor to consider in this field. Although in clinical trials oral bisphosphonates have generally demonstrated a safety profile similar to placebo, in clinical practice patients may experience upper gastro-intestinal adverse events, another primary reason cited for patients discontinuing bisphosphonates treatment. A telephone survey conducted in 956 women receiving hormone replacement therapy (HRT), raloxifene or alendronate, explored this issue. At the time of interview, 19% had stopped therapy. Side effects and safety concerns were the primary reasons stated for discontinuing therapy, with 46% experiencing upper gastro-intestinal events.

Another important factor influencing adherence is the cost of medication. On the basis of an evaluation of claims data, Caro et al. suggest that adherence and persistence may be strongly influenced by cost and availability of insurance coverage. A study conducted in Israel showed that the number of women on osteoporosis medication and persistence with therapy increased when co-pays were eliminated for osteoporosis medication specifically. However, even good insurance prescription coverage does not necessarily guarantee that people with a chronic, asymptomatic disease will take their medications over the long term.

### **Strategies to Enhance Adherence to Osteoporosis Medication**

One strategy to improve compliance is to increase patient convenience by decreasing the frequency of dosing regimens. In a review of 76 studies across a variety of therapeutic areas, Claxton et al. concluded that less frequent dosing regimens significantly improve compliance. Alendronate and risedronate were initially introduced as once-daily formulations, but are now both available as once-weekly formulations. These formulations reduce the inconvenience of having to take the bisphosphonate in the morning, fasting and remaining upright after dosing, to once-weekly instead of daily. However, and as mentioned above, the adherence to weekly regimens remains suboptimal. Less frequent regimens, such as once-monthly or once-yearly administration may increase patient convenience and therefore potentially improve compliance and achieve the full potential benefit of bisphosphonate therapy. Two clinical studies (Boniva Alendronate

Trial in Osteoporosis (BALTO I and II)) of patient preference demonstrated that more than 70% of patients preferred treatment with the monthly regimen of ibandronate versus the weekly regimen of alendronate. The results from the PERSIST (Persistence Study of Ibandronate verSUS alendronaTe) trial showed that once-monthly ibandronate, coupled with a patient support programme, improved persistence on treatment, compared with once-weekly alendronate.

Enhancing communication between the physician and the patient is a key and effective strategy in boosting the patient's ability to follow a medication regimen. However, it was highlighted that there is a serious and widespread lack of communication between physicians and patients about the need to stay on long-term treatment in order to effectively treat osteoporosis and reduce the risk of fractures.

Data from the IMPACT study showed increased persistence in those patients receiving a positive message based on bone resorption marker monitoring. In a study conducted by Silverman et al., 140 women were randomised to receive educational information and a voucher for immediate BMD testing in one year. Among women who received an immediate BMD test, 63.4% filled their prescription immediately. In contrast, only 20% of those who received a BMD test one year later filled their prescription. In a recent UK study, both nurse monitoring alone and nurse plus bone turnover measurement monitoring improved adherence by 57%. This demonstrates that discussion with a healthcare professional to reinforce the need for long-term therapy may be of equal value for patient compliance as information about response to biochemical markers. Similarly, Cooper et al. reported the success of patient support programmes plus monthly ibandronate in improving persistence compared to a weekly bisphosphonate only.

### **Conclusion**

Adherence to osteoporosis medications remains poor and is associated with long-term consequences such as increased osteoporotic fractures and healthcare costs. Pursuing interventions that could improve adherence is worthwhile. The development of new medications with extended dosing intervals and interventions to involve patients in the treatment of their diseases may promote compliance and enhance patient satisfaction and outcomes. ■

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