

What can be done to maximize adherence of bisphosphonates in patients with osteoporosis?

“...improved adherence to bisphosphonate therapy will be achieved via a parallel 3D approach...”

KEYWORDS: adherence ■ bisphosphonates ■ compliance ■ fracture ■ osteoporosis ■ persistence

Osteoporosis affects more than 200 million people worldwide [1] and its prevalence is expected to increase along with an aging population. The overall lifetime risk of an osteoporotic fracture is approximately 50% for women and 20% for men [2], which is comparable to that of cardiovascular disease and higher than that of cancers, including breast cancer. Bisphosphonates represent the mainstay of osteoporosis management. The results of several controlled clinical trials have shown that treatment with bisphosphonates increases bone mineral density, reduces bone resorption and hence decreases the risk of osteoporotic fractures [3]. However, the efficacy observed in clinical trials does not translate to real-life effectiveness in routine clinical care. The data in the literature have shown that, despite the availability of effective treatments, osteoporosis continues to plague western society and osteoporotic fractures remain a leading cause of mortality and burden of illness among the older population, with a significant economic and social impact. In addition to the fact that patients participating in controlled clinical trials are highly selected and managed under ideal conditions, variation with respect to physician decision-making and attitudes, as well as access to care, contribute to this treatment gap. Suboptimal adherence to treatment regimens has also been recognized as the most important patient-centric and perhaps amenable factor causing reduced effectiveness of marketed treatments for chronic conditions, including osteoporosis.

A recent retrospective study utilizing long-term data from provincial health insurance claims databases in Canada showed that among the 636,114 patients treated with oral bisphosphonates between 1996 and 2009, 36% discontinued treatment within 2 years, while 13, 17 and 24%

discontinued treatment by 3, 6 and 12 months, respectively [4]. Furthermore, of these patients, only 50% were compliant and 41% were persistent during that period demonstrating low adherence with oral bisphosphonates in real life. In this context compliance refers to percentage of the time period with coverage by available medication as measured by the medication possession ratio, and persistence refers to the absence of clinically significant gaps in prescription refills. These results are in agreement with those reported in other countries suggesting that the problem of nonadherence is not population specific [5,6].

The association between poor adherence with oral bisphosphonates and short- to medium-term increased risk in osteoporotic fractures is well established [7]. However, in the above study in which the cohort was followed for up to 14 years, the association between low adherence and risk of fractures was found to become augmented with longer disease duration [4]. More specifically, non-compliance was associated with an increased risk for a fracture of 8% after 2 years compared with 23% after 14 years, indicating that interventions aimed at improving long-term adherence should be implemented.

Suboptimal adherence to medications, and in particular those used for chronic conditions, is a widespread problem causing significant burden of illness to society, affecting patients and healthcare systems. From an economic perspective, unused dispensed medications represent a major expenditure [8]; a recent study in Sweden estimated that the cost related to nonadherence was approximately 40–50% of the total medication acquisition costs [9]. Furthermore, fractures occurring due to poor adherence with bisphosphonate treatment results in unnecessary direct and indirect costs due to hospitalizations,



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physician visits, additional treatments, work absenteeism and productivity loss. Previous studies have shown that at least 10% of hospital admissions and 25% of nursing home admissions are due to nonadherence with treatment in chronic asymptomatic diseases [10]. In the USA alone, nonadherence with medications has been estimated to incur at least US\$290 billion in avoidable medical expenses annually [11].

Reasons for poor adherence

The cause of poor adherence with bisphosphonate treatment is multifactorial, involving interactions between access of care, physician attitudes and treatment patterns, type of treatment regimens used and patient-centric factors, including education, duration of disease, history of fractures, polypharmacy, concomitant medication use and comorbidities, tolerability and adverse event experience, and patient perception and attitudes towards treatment.

■ Access of care

Accessibility of treatment and prescription medications is often a factor of poor adherence among the elderly and individuals in lower socioeconomic strata. Given that osteoporosis is asymptomatic and its management is essentially a preventive intervention, patients with modest resources or limited insurance coverage may choose to forego their osteoporosis medication in favor of other treatments. Therefore, it is essential that effective treatments for osteoporosis are adequately covered by health insurance plans across all socioeconomic strata.

■ Physician attitudes & treatment patterns

Physicians, in general, do not practice disease management but rather engage in one-dimensional patient treatment. Disease management requires that the physician not only prescribes the medication but intervenes in order to ensure that the patient achieves optimal adherence to the treatment. However, the erroneous presumption made by contemporary prescribers is that the patients will fill their prescriptions and will take their medications as instructed without any need for further interventions. This is despite the fact that epidemiological- and population-based studies have shown that patients do not adhere to treatments for chronic conditions. Physicians and healthcare providers need to alter their practice patterns to encompass interventions that will identify causes and, hence, personalize solutions for suboptimal treatment adherence for individual patients.

■ Treatment regimen

Medication adherence is directly associated with the therapeutic regimen. More specifically, the frequency of drug administration has been shown to be inversely correlated with medication adherence [12]. Less frequent dosing results in better compliance and persistence with bisphosphonates, but adherence is still suboptimal [13]. Weekly bisphosphonate regimens are preferred to daily regimens and are more likely to achieve greater long-term compliance [14]. Once-monthly oral bisphosphonate was associated with a 47% improvement in persistence at 6 months compared with a once-weekly regimen [15] and once-quarterly intravenous administration resulted in greater adherence compared with oral monthly administration [16]. Data on the adherence with the more recent once-yearly intravenous zoledronic acid are still scarce; however, it is conceivable that the once-yearly application would potentially guarantee adherence for at least 12 months and therapeutic coverage for approximately 15 months.

A common problem with adherence with oral bisphosphonates is related to their strict administration instructions. In order to achieve maximal bioavailability and ensure upper gastrointestinal tolerability, patients have to fast overnight before receiving bisphosphonates and for a further 30 min after administration, take their medication with water only and maintain an upright position after administration. Any deviation from these complex instructions may negatively affect therapeutic outcomes and increase the risk for upper gastrointestinal adverse events.

Given the above, it follows that bisphosphonate treatments that are less complicated to administer with more patient-friendly schedules should be preferred in order to reduce the risk of poor adherence.

■ Patient education

In the absence of fractures, osteoporosis is largely asymptomatic. As a result, it is difficult for patients to realize the effects of poor adherence. In accordance, patients with a previous osteoporotic fracture are more likely to adhere to treatment [17]. Previous studies in other chronic diseases have shown that therapeutic adherence is influenced by patient knowledge and understanding of their condition and treatment, as well as their interpretation of benefits and risks associated with their treatment [18]. In a cross-sectional survey of patients with osteoporosis on bisphosphonate therapy, patient concerns about their medication, such as fear of addiction

and fear of taking the medication over a long period of time, were found to increase the risk of nonadherence [17]. Therefore, it is essential to increase patient involvement in their management by improving their understanding of the association between adherence to treatment and bone density, the relationship between the latter and the risk of fractures, and the consequences of fractures. Facilitating direct patient involvement in their treatment is an integral part of chronic disease management that will have a positive effect on adherence to treatment.

Patient support programs assuming the pedagogical role of informing osteoporosis patients on the pathology of their disease, the mechanism of action and adverse effects of bisphosphonates, and the risks associated with nonadherence, as well as addressing their potential concerns could play a pivotal role in increasing the long-term adherence with bisphosphonates. Physicians and/or nurses could also play an important role in patient education. It is conceivable that in a real-life clinical setting less-frequent and less-stringent monitoring are feasible compared with those used in controlled clinical trials. However, considering that the majority of medication withdrawals occur within a few months of beginning therapy [4,19], a strategy where closer follow-up, monitoring of adherence and patient education are adopted at this important stage could be envisioned.

In line with this approach, WHO has recommended the 'TRIAD' model, a collaborative partnership between patients and families, healthcare teams and community supporters, to improve adherence with chronic treatment. This model emphasizes the importance of communication and cooperation between all members of the TRIAD in order to increase motivation and, as a result, clinical outcomes. The possible role of closer monitoring of adherence [20] or patient education [21] has been evaluated in previous randomized trials without showing a significant effect. However, the possible effect of these interventions may have been masked by the artificially frequent follow-up schedule that enhances patient alertness, the selection of 'ideal' patients who are highly adherent regardless of imposing an intervention, as well as the 'halo' effect where patients participating in a trial modify their normal behavior (in this case becoming highly adherent in the absence of an intervention).

■ Nonmodifiable factors

The above discussion focused on factors that are associated with bisphosphonate treatment adherence that are potentially modifiable. Other

factors that affect adherence to treatment are nonmodifiable and include longer disease duration, concerns for, or history of, adverse events or low tolerability, comorbidity, concomitant medication use and polypharmacy. Despite the fact that these factors are not modifiable, screening and detection of these should be considered in order to identify patients that are at high risk for low bisphosphonate treatment adherence. Appropriate interventions should be applied for these patients to mitigate the effect of these factors and increase adherence.

Increasing adherence to bisphosphonate treatment

The previous discussion has identified modifiable factors that are associated with adherence to bisphosphonate treatment for the management of osteoporosis. Interventions aimed at healthcare providers, patients and treatment regimens themselves can affect these factors towards optimizing adherence to bisphosphonate treatment. However, none of these interventions could be effective if applied in isolation. More specifically, improving adherence to bisphosphonate treatment requires a multifactorial approach that is compatible with the multifactorial cause of suboptimal adherence.

In summary, improved adherence to bisphosphonate therapy will be achieved via a parallel 3D approach that will include:

- Modification of physician treatment patterns to a disease management approach;
- Changing the patient's role from a passive recipient of treatment to an active participant through education and continuous feedback;
- Use of simplified treatment regimens that facilitate administration and enhance adherence.

Increasing the patient's knowledge of the disease and explaining the importance of intervening therapeutically represents another area of opportunity.

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