

# Adherence to anti-osteoporotic treatment: does it really matter?

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In osteoporosis, the level of perceived threat to health often does not motivate the patient to comply with therapy. Furthermore, few benefits from treatment are directly perceived by the patient. Therefore, adherence to anti-osteoporotic treatment is low, with more than 20% suspending their treatment before 6 months of therapy have passed. This results in less beneficial effects on bone turnover and bone mineral density and an increased risk of spine or hip fracture. Low adherence to anti-osteoporosis medication fails to lower the burden of the disease. The pharmaceutical industry may have to convince health policymakers that beneficial outcomes observed during randomized controlled trials (a setting with artificially enhanced adherence), translate favorably in real life settings. This applies to several therapeutic areas (antihypertensive drugs, cholesterol-lowering agents etc.) where similar compliance problems are seen. In the future, marketing authorization and/or reimbursement could only be granted to medications that demonstrate an effectiveness of similar magnitude to their efficacy.

Poor adherence to medications, particularly those used to treat chronic diseases, is a widespread problem that is associated with an enormous burden on patients and health-service resources [1]. Whereas recent claims were made that the language used to describe how patients take their medications needs to be reassessed [2], the term 'adherence' will be used here to imply both compliance and persistence. In terms of compliance, in other words, how often patients take medications correctly, several studies estimate that only approximately half of patients comply optimally with long-term treatment, regardless of their therapeutic area [3,4]. One in five patients do not even redeem their prescription [5]. With regards to persistence – how long patients continue to take medications – studies in a number of chronic conditions have shown that persistence with treatment deteriorates over time [6,7].

Before the occurrence of fractures, the level of perceived threat to health often does not motivate the osteoporotic patient to comply with therapy [8]. In addition, anti-osteoporosis treatment needs to be prescribed during several months or years to be effective, and the patients usually do not perceive any clinically relevant benefit from the treatment [8,9]. Therefore, it appears quite reasonable to question whether the results observed in clinical trials assessing the antifracture efficacy of osteoporosis medications (a setting generally associated with a remarkably high rate of adherence [2]) can be extrapolated to the use of these medications in a real-life setting.

The clinical and financial consequences of low adherence to anti-osteoporotic medications in daily practice should be carefully monitored. A provocative question at this stage would be for healthcare policymakers to reassess the interest of covering medications. For this, the efficacy derived from clinical trials could be jeopardized by a poor rate of adherence when used in the general osteoporotic population.

## Adherence & outcomes in antiresorptive therapy

Several medications have now shown their ability to reduce fracture rate, at the axial and/or appendicular skeleton, in postmenopausal osteoporotic women [10]. Studies assessing the impact of high/low adherence to anti-osteoporotic medications on fracture risk were almost exclusively conducted with antiresorptive medications. Several studies showed that at least 20% of the women prescribed with raloxifene or bisphosphonates discontinue treatment during the initial 6 months of therapy [1,11–13]. A large US database of 58,109 osteoporotic patients, who initiated drug therapy for osteoporosis, reported a 1-year compliance rate below 25% for all osteoporosis therapies [14]. In a longitudinal cohort of 211,319 patients who received bisphosphonate prescription from 14,000 US retail pharmacies, only about one third of patients receiving a daily dose and fewer than half of those receiving weekly formulations achieved adequate adherence. This is defined here as a medication

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possession ratio (MPR = days of supply/365 days) of 80% or above [15]. Patients new to bisphosphonates had the worst medication adherence over the year of follow-up (25.2% for weekly and 13.2% for daily dosing) [15].

In the Canadian Database of Osteoporosis and Osteopenia (CANDOO), persistence with bisphosphonates decreased with time. 29.9% and 35.8% of alendronate users discontinued their medication after 1 and 2 years, respectively [16]. Persistence rates in this study may be artificially high. Although the study took place in a clinic, patients were given written and verbal encouragement to continue with medication, which would be unlikely to occur in normal clinical practice and can be expected to increase adherence. The apparent persistence rate may also have been elevated, since the study database only captured data from patients who returned for a follow-up visit. Patients who return for follow-ups may be more likely to persist with medications than those who did not return [1].

The impact of suboptimal adherence on osteoporosis outcomes has been examined in a number of recent studies. Adherence of 75 osteopenic or osteoporotic women to raloxifene was significantly correlated with a decrease in urinary *N*-telopeptide of Type I collagen, a marker of bone resorption and an increase in femoral bone mineral density (BMD) [17]. Yood and colleagues found that the percentage increase in spinal hip BMD was significantly greater among patients with 66% or more compliance with estrogens or bisphosphonate therapy, compared with lower compliance, in 176 patients with osteoporosis followed for a mean of 590 days [18]. Analysis of outcomes among 11,249 women with osteoporosis in the Saskatchewan health data files showed that adherence to osteoporosis medications of less than 80% was associated with a significant increase in the risk of fracture (hazard ratio = 1.16;  $p < 0.005$ ) on multivariate analysis [19]. In the above-referenced study, analyzing a large Californian health insurance database [14], low compliance significantly reduced the risk of hip (odds ratio = 0.382) and vertebral (odds ratio = 0.601) fractures compared with the more compliant patients. Furthermore, compliant patients used fewer physician services, hospital out-patient services and hospital care [14]. Patients whose plasma strontium levels suggest an appropriate intake of strontium ranelate are also those presenting with the most marked

reduction in the risk of hip fracture [20]. These results were in accordance with previous reports of a profound negative effect on healthcare systems, caused by poor adherence, including amounts of unused prescriptions, increased visits to healthcare providers, unnecessary treatment costs (e.g., for changes in prescribed agents) and admission to care because of associated treatment failures; in the latter, it was established that such treatment failures in chronic disorders account for 10% of hospital admission and 20% of admission to nursing homes in the USA [21].

It should also be kept in mind that efficacy of currently used fracture preventive treatments was demonstrated in the presence of calcium and vitamin D supplementation, therefore adherence to these supplements is indispensable.

## Conclusion

The WHO recently issued an evidence-based guide for clinicians, healthcare managers and policy makers to improve strategies of medication adherence [21]. In this document, adherence is defined as a complex behavioral process determined by several interacting factors. These include attributes of the patient's environment (that comprises social supports, characteristics of the healthcare system, functioning of the healthcare team and the availability and accessibility of healthcare resources) and characteristics of the disease in question and its treatment [22]. It is also of critical importance to differentiate between intentional and nonintentional adherence. Nonintentional adherence is associated with regimen complexity, memory, electronic and other forms of monitoring, among others. Intentional nonadherence is associated with beliefs regarding medications, beliefs concerning susceptibility and severity of the illness and trade offs between treatment efficacy and risks. The latter is the key factor in adherence. In osteoporosis, patients monitored by nurses or monitored using graphings of response to treatment (assessed by biochemical markers of bone turnover) have a 57% improvement in adherence to raloxifene compared with patients receiving no monitoring [17]. Appropriate adherence to osteoporosis treatment has been associated, in a multiracial round of US focus groups, with recognition of the serious consequences of non-adherence, realization of the beneficial effects, reasonable cost of treatment and the belief that medicines are not harmful. Patient values (e.g., unwillingness to admit having a disease

that requires treatment) also play a big role here. Doubts about physicians' competence to prescribe appropriate drugs have also been expressed [23]. In similar studies, conducted to identify patients' preferences in the management of osteoarthritis, the risk of toxicity associated with a particular medication was a predominant factor in the willingness to pay for the medication; a substantial subset of the population being willing to forgo treatment effectiveness for a lower risk of adverse effects [24,25].

#### Future perspective

Improving adherence is, thus, the combined responsibility of the policymakers and of the pharmaceutical industry. Defraying drug cost by policymakers would certainly help to increase long-term persistence. There is no doubt that better labels and package inserts can help people to increase their nonintentional adherence [22]. However, based on the above-mentioned expression of patients' preferences, the development of drugs with few side effects and easy, or easier, administration routes or regimens would promote intentional adherence. It has been found, across a range of therapeutic areas, that adherence with medications is inversely related to frequency of dosing [26]. Osteoporosis patients are attracted by drugs with a convenient regimen of administration, such as weekly dosing [27] or with the interval

between doses longer than a week. This could be the case for oral monthly ibandronate, once every 3 months injection of ibandronate, once yearly zoledronate or once every 6 months Amgen (AMG) 162. In an osteoporosis market with an annual turnover amounting close to US\$5 billion, it can be expected that health policymakers will be more stringent in their requirements before granting marketing authorization/reimbursement to medications that request long-term use and optimal adherence to reduce fractures. For previously registered/reimbursed medications, postmarketing studies might be required to demonstrate adequacy between the results observed in clinical trials and those obtained in real life settings. It is unlikely that the antifracture efficacy of the currently developed medications, with dosing intervals higher than weekly and which will be derived from their pivotal randomized double-blind studies, will significantly outrage the effect observed, in similar conditions, for the currently registered drugs. Thus, the real challenge for these new chemical entities will be to demonstrate that their user-friendly regimen impacts, in a clinically relevant manner, on the long-term adherence and related outcomes for the patients. Adherence to treatment in patients that have sustained a hip fracture also deserves special attention, since this is a high-risk population that has a specific problem that should be

### Executive summary

#### Introduction

- Poor adherence to medications is a widespread problem that is associated with an enormous burden on patient and health-service resources.
- The silent character of osteoporosis and the absence of perceived benefits for the patient decrease long-term compliance to and persistence with anti-osteoporotic medications.

#### Outcomes in osteoporosis treatment

- More than 20% of the patients receiving anti-osteoporotic medications quit therapy before the end of the sixth month.
- Less than 50% of patients initiating a bisphosphonate treatment are still compliant at the end of the first year.
- Weekly bisphosphonates improve the situation but compliance remains suboptimal.
- Low adherence to anti-osteoporotic medications significantly decreases the benefit observed on bone mineral density and fails to decrease the risk of vertebral and femoral fractures.

#### Perspectives

- Adherence is an important modifier of health system effectiveness.
- Adherence is influenced simultaneously by several factors.
- A multidisciplinary approach toward adherence is needed.
- Medications used in osteoporosis could be requested to demonstrate an antifracture efficacy of a similar magnitude in clinical trials and in real life settings.

#### Conclusion

- Registration or reimbursement of chronic medications could be limited to chemical entities having demonstrated their overall effectiveness, a global concept in which adherence and related outcomes may play a significant role.

addressed. Whereas the organized osteoporosis disease management program was shown to significantly decrease total direct costs of osteoporosis despite adherence issues [28], the pharmaceutical industry might have to convince health managers (health maintenance

organizations and reimbursement commissions in countries with drug coverage etc.) to select drugs to be covered on the basis of their overall effectiveness, a global concept in which adherence and related outcomes may play a significant role.

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