Expert Opinion

Poor adherence to oral bisphosphonate treatment and its consequences: a review of the evidence

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Poor therapeutic adherence is a major issue faced by physicians today. This paper summarizes the adherence rates with oral bisphosphonate (OBP) treatment in clinical practice and their impact on clinical outcomes. Studies systematically demonstrated that overall compliance and persistence with OBPs among osteoporotic women are poor. Although extending dosing intervals improved adherence, the gains are suboptimal. Most importantly, low compliance and persistence rates consistently resulted in increased rates of fractures. The results emphasize the importance of adherence to treatment to achieve optimal antifracture efficacy. There is an urgent need to implement strategies and to encourage physicians to take measures that increase patients' awareness of the need to use osteoporosis medications as directed in order to benefit from them fully.

Keywords: adherence, bisphosphonates, compliance, fracture, osteoporosis, persistence

Expert Opin. Pharmacother. (2009) 10(14):2303-2315

1. Introduction

Increased life expectancy has resulted in the emergence of age-related fragility fractures as a major public health problem, with a lifetime risk of hip, vertebral and other peripheral fractures of 40 – 50% for women and 13 – 22% for men [1]. The estimated worldwide number of new osteoporotic fractures for the year 2000 was 9 million, of which 1.6 million were at the hip, 1.7 million at the distal forearm and 1.4 million clinical vertebral fractures [2]. These fractures are associated with an increase in morbidity and mortality that imposes a huge healthcare burden on the community. Up to 50% of women who sustain a hip fracture become dependent on others for activities of daily living, about 20% will die within 1 year and about the same percentage will require long-term care [3-5]. The estimated annual expenditure related to osteoporotic fractures was $17 billion in the USA in 2001, and €30 billion in Europe [6].

In recent years there has been an explosion in the development of new drugs for the treatment of osteoporosis. Pharmacological interventions approved in the USA and/or the EU for the treatment and/or prevention of osteoporosis in postmenopausal women include amino-bisphosphonates (e.g., ibandronate, alendronate, risedronate and zoledronic acid), non-amino-bisphosphonates (etidronate), the selective estrogen-receptor modulator (raloxifene), strontium ranelate, teriparatide (recombinant 1 – 34 human parathyroid hormone), calcitonin and estrogen/hormone replacement therapy (HRT).

Oral amino-bisphosphonates (OBPs) are firmly established as a first-line therapy with clinical trials having demonstrated that treatment significantly reduces the incidence of both vertebral and nonvertebral fractures. In placebo-controlled trials of alendronate and risedronate, the relative risk reduction for vertebral fractures has been reported as 50 – 60%, for hip fractures as 44 – 60%, and for nonvertebral

10.1517/14656560903140533 © 2009 Informa UK Ltd ISSN 1465-6566

fractures as 51% [7-10]. For daily ibandronate users, the risk of new vertebral fractures was reduced by up to 62% [11].

Although OBPs are the most potent of the currently approved antiresorptive agents, accumulating evidence indicates, however, that these agents are underutilized in clinical practice owing to low rates of prescribing to patients at high risk of fracture [12-16] and poor drug adherence among those who have been prescribed such therapy [17-25]. The literature suggests that about 50% of patients are poorly compliant or poorly persistent within 12 months of initiating treatment. This inadequate therapeutic adherence to OBPs in the treatment of osteoporosis compromises therapeutic outcomes, resulting in lower bone mineral density (BMD) gains [26,27], reduced effects on bone turnover [28] and subsequently increased fractures rates [21-25,29]. Moreover, poor adherence has a profound negative effect on healthcare systems, including increased 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 failure [29-34].

Therefore, it is important for healthcare providers to understand why nonadherence to osteoporosis medication occurs and to encourage and implement strategies that increase adherence.

The aim of this review was to summarize the levels of patient compliance and persistence with OBPs treatment as well as the consequences of poor compliance and persistence in real-life settings.

2. Materials and methods

We conducted an electronic search in PubMed (which includes citations from MEDLINE and other life science journals for biomedical articles) for citations of relevant articles accessible between January 1995 and February 2009, using the following keywords: bisphosphonates, alendronate, risedronate, ibandronate, persistence, compliance, adherence, osteoporosis, medication, medication possession ratio, database, prescription, and fracture. The search was restricted to English-language results.

We included all observational and/or retrospective analyses that examined either patient compliance or persistence or both with OBP treatment, as well as those who evaluated the relationship between compliance and/or persistence with bisphosphonates treatment and postmenopausal osteoporotic fracture risk in clinical practice. Articles were excluded if they evaluated adherence to drug therapy for conditions other than osteoporosis. The following publication types were also excluded: randomized controlled trials, reviews, editorials, letters and case reports. We excluded randomized controlled trials because they are more controlled and rigorous and could increase adherence in a way that might not reflect real-life settings. Bibliographies of included articles were also checked to identify other relevant studies.

Literature searches reveal that definitions of compliance, persistence and adherence vary between publications. These terms were consistently used interchangeably in much of the literature, despite differences in their meanings. For the purpose of this review, the definitions from the International Society for Pharmacoeconomics and Outcomes Research for persistence and compliance were used. Persistence is defined as the accumulation of time from initiation to discontinuation of therapy [35]. Compliance reflects the extent to which the patient takes the medication in accordance with the prescribed dose and interval use as specified in the official product information. Adherence is a general term encompassing the combination of the two.

3. Results

Thirty-nine publications and congress abstracts were identified for inclusion in the current review [17-29,33,34,36-59]. Fifteen assessed only persistence [17,20,23,33,36-42,46,47,52,53] and 12 studies assessed only compliance [18,21,24,27-29,49-51,54-56]. Eleven studies examined both persistence and compliance [19,22,25,26,34,44,45,48,57-59]. Fifteen studies contained data from other osteoporosis medications in addition to bisphosphonates [21,26,33,34,36-42,48,54,56,58]. Twenty-four studies contained persistence and/or compliance data for OBP therapy only [17-20,22-25,27-29,43-47,49-53,55,57,59]. Persistence and/or compliance data for daily, weekly or monthly OBPs were compared in 12 studies [17-19,23,25,43-47,52,55].

We identified 19 studies investigating the relationship between adherence and its impact on outcomes [21-29,33,34,52-59]. Among them, 11 studies investigated the decrease in fracture risk associated with either compliance [21,24,29,34,54-56] or persistence [23,33,52,53]. Only five studies had specifically examined the association of both compliance and persistence with treatment and fracture risk reduction [22,25,57-59].

3.1 Adherence rates

In this section, we report studies that investigated only persistence and/or compliance with treatment. The studies that assessed, besides adherence rates, the impact of adherence on outcomes are presented in the next section.

Using a telephone survey, Tosteson and colleagues interviewed 956 women who had osteopenia or osteoporosis and who had been started on therapy [36]. Approximately one-quarter (19 – 26%) of patients abandoned osteoporosis therapy within 7 months. More than two-thirds of women who discontinued reported doing so because of side effects. After adjustment for adverse events, early discontinuation of therapy did not differ significantly between alendronate, raloxifene and HRT. This study is limited because it was based on self-report and may overestimate adherence.

Turbi *et al.*, in a multicenter observational study, examined discontinuation rates for postmenopausal women treated with raloxifene and compared them with those of women receiving alendronate [37]. In the first 3 months, 13% of patients taking alendronate did not continue the initially assigned treatment, which was significantly higher than the

rate in the raloxifene group (5%). However, after 3 months, no significant difference was found between the two groups with regard to treatment compliance.

In a nationwide Italian survey carried out in osteoporosis clinics, Rossini *et al.* found that once-weekly alendronate had the lowest discontinuation rate (7%) of all therapies evaluated [38]. Discontinuation rates for alendronate once daily and risedronate once daily were 21% and 19%, respectively. The discontinuation rate for raloxifene was 16%.

In a small group of patients (n = 178), Segal *et al.* evaluated persistence to treatment with alendronate or raloxifene [39]. The discontinuation rate after only 6 months was 23% overall, 31% in the raloxifene group and 18% in the alendronate group (NS).

An analysis of the Canadian Database of Osteoporosis and Osteopenia (CANDOO) also revealed that persistence with current OBPs decreases over time [40]. After one and two years of being prescribed treatment, 14.5% and 19.1% of patients discontinued etidronate, while 29.9% and 35.8% of patients discontinued daily alendronate.

In a pharmacy claims database study, Solomon *et al.* showed that 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 [41]. Compliance was defined as medication available > 66% of the time for a 60-day period. They also examined predictors of medication adherence. Characteristics that predicted compliance were female gender, younger age, fewer comorbid conditions, history of previous fracture, fewer medications, BMD testing and nursing home residency.

Lo *et al.* examined data collected from Kaiser Permanente of Northern California [20]. The study included women newly prescribed weekly alendronate. Persistence was analyzed with refill gaps of different lengths (30, 60 and 120 days). The discontinuation rate for 1 year was 58% with a 30-day gap, 49.6% with a 60-day gap and 42.2% with a 120-day gap. About one-third of patients who were nonpersistent restarted alendronate or another osteoporosis medication within 6 months. Similarly, in a large cohort study involving 26,636 new users of an osteoporosis medication (alendronate, risedronate, raloxifene, estrogen), Brookhart *et al.* found that among patients who stopped therapy for at least 60 days, an estimated 30% restarted treatment within 6 months and 50% restarted within 2 years [42].

Ettinger *et al.* examined persistence with OBP use to test the hypothesis that women taking bisphosphonates with longer intervals between doses would be more persistent, using data from a large US pharmacy claims database [17]. At 1 year, only 15.7% of new daily users and 31.4% of new weekly users were still on therapy ($p < 0.001$). Among women continuing bisphosphonate treatment, 39% of patients taking daily bisphosphonate and 58.5% of weekly users remained on medication at the end of 1 year ($p < 0.001$).

In a longitudinal cohort of 211,319 patients who received OBPs on prescription, only about one-third of patients receiving a daily dose and fewer than half of those receiving weekly formulations achieved adequate compliance [18]. Compliance was assessed using the medication possession ratio (MPR) by dividing the sum of all days of OBP supply received during the 1-year study period divided by 365 potential days of OBP therapy. The mean MPR at 12 months was 65% in the weekly regime group compared with 54% in the daily regimen group ($p < 0.001$). The lowest proportion of adequately compliant patients (MPR ≥ 80%) was among new users of OBPs over the year of follow-up (25.2% for weekly and 13.2% for daily dosing, $p < 0.001$).

Brankin *et al.* examined three UK GP-sourced databases: the General Practice Research Database (GPRD), IMS Disease Analyzer (MEDIPLUS), and the Doctors Independent Network database (DIN-LINK) [43]. Overall compliance, defined by mean MPR, was 74% in the General Practice Research Database, 68% in the MEDIPLUS study and 59% in the Independent Network database study. Analyses from all three databases demonstrated that patients receiving weekly therapy were more compliant with their treatment regimen compared with those receiving daily treatment.

A study using the German Mediplus database compared the adherence of patients to daily and weekly treatment with OBPs [44]. Compliance quantified using the parameter MPR was 51.7% in the weekly regimen group versus 37.7% in the daily regime group at 1 year. After 12 months, 54.5% of patients in the weekly group discontinued therapy compared with 72.2% of patients in the daily group ($p < 0.01$).

Another study compared daily with weekly OBP dosing regimens in a vast cohort of women in the USA who had been on OBP therapy for at least 6 months [19]. Of the 2741 patients included, 44.2% with weekly dosing compared with 31.7% with daily dosing were persistent (> 30-day gap between 2 refills) at 12 months ($p < 0.0001$). Mean persistence was 226.8 days with weekly dosing and 185.4 days with daily dosing. Compliance was better with weekly dosing (69.2%) than with daily dosing (57.6%; $p < 0.0001$). Compliance was satisfactory (> 80%) in only 40.4% of patients on the daily regimen compared with 55.3% of those on the weekly regimen.

Using a 45-day gap in medication coverage to define lack of persistence with OBPs in a pharmacy database, Boccuzzi *et al.* reported that only 18% of daily users and 22% of weekly users were persistent with treatment at 12 months [45]. Compliance was 53.8% with daily dosing and 62.5% with weekly dosing. Compliance rates of less than 75% were noted in 64.5% of patients on weekly dosing and 52.8% of those on daily dosing.

Silverman and colleagues found consistent patterns of persistence using two different managed care claims databases with once-monthly ibandronate and once-weekly OBPs [46]. Depending on the database, patients taking monthly ibandronate were either 37.7% (HR = 0.623, 95% CI 0.575 – 0676; $p < 0.001$) less likely or 25.1% (HR = 0.749, 95% CI 0.702 – 0.796; $p < 0.001$) less likely to discontinue therapy than patients taking

Table 1. Persistence to oral bisphosphonates (OBPs) at 12 months.

Ref.	Persistence definition	% of persistent patients
Ettinger *et al*. [17]	No. of patients on therapy for each month divided by no. of patients who were on therapy in month 1	39% for daily OBP regimen 58.5% for weekly OBP regimen
Cramer *et al*. [19]	Refill gap ≤ 30 days	31.7% for daily OBP regimen 44.2% for weekly OBP regimen
Bart *et al*. [44]	No more prescriptions until end of the follow-up	27.8% for daily OBP regimen 45.5% for weekly OBP regimen
Boccuzzi *et al*. [45]	Refill gap ≤ 45 days	18% for daily OBP regimen 22% for weekly OBP regimen
Silverman *et al*. [46]	Refill gap ≤ 30 days	26.9% for weekly OBP regimen 36.3% for monthly OBP regimen
Gold *et al*. [52]	Refill gap ≤ 30 days	16% for daily OBPs* regimen 24% for weekly OBP* regimen
Lo *et al*. [20]	Refill gap ≤ 30 days Refill gap ≤ 60 days Refill gap ≤ 120 days	58% for weekly OBP regimen 49.6% for weekly OBP regimen 42.2% for weekly OBP regimen
Boccuzzi *et al*. [48]	Refill gap ≤ 45 days	21% for alendronate 19% for risedronate
McCombs *et al*. [33]	Uninterrupted therapy for 12 months (refill gap ≤ 14 days)	24% for all OBP regimens
Van den Boogaard *et al*. [23]	Uninterrupted therapy for 12 or 24 months (refill gap ≤ 50% of the period of the given dispensing or 7 days)	43.6% for all OBP regimens 27.4% for all OBP regimens*
Siris *et al*. [22]	Refill gap ≤ 30 days	20% for all OBP regimens*
Rabenda *et al*. [25]	Refill gap ≤ 35 days	39.5% for all OBP regimens

*The reported persistence rates were at 24 months.

weekly OBP therapy. The 12-month persistence rates were 36.3% for patients receiving monthly ibandronate and 26.9% for patients receiving weekly OBPs ($p = 0.003$). In the other database, the 12-month persistence rates were quite similar (35.7% vs 24.8%, $p < 0.001$).

Cooper *et al*. reported that the proportion of persistent patients (defined using a refill gap of < 14 days) with treatment at 6 months was 56.6% with monthly ibandronate versus 38.6% with weekly alendronate [47]. However, the higher persistence with ibandronate could have been the result of a patient support program with a monthly telephone reminder provided to the ibandronate group only.

In another study, Boccuzzi *et al*. conducted a database study of compliance and persistence in 10,566 women who started taking various osteoporosis medications [48]. Compliance over 1 year was 61% with alendronate, 58% with risedronate and 54% with raloxifene; corresponding figures for persistence were 21.3%, 19.4% and 16.2%, respectively. Mean time to treatment discontinuation was not significantly different across the three groups (2.5 months). This study provides additional evidence that adherence with osteoporosis medications is relatively low, with no major differences across drugs.

All studies reported low rates of compliance and/or persistence. **Table 1** shows the levels of persistence with OBPs at 12 months reported across studies. In **Figure 1**, we report the mean MPR for OBPs at 12 months, whereas **Figure 2** shows the proportion of patients with adequate compliance (≥ 80%) at 12 months. In **Table 1** and in **Figures 1** and **2**, we report only compliance and/or persistence rates for studies using data from claims or pharmacy databases and for which compliance and/or persistence rates included only OBPs. In fact, for some studies, the reported rates included, besides OBPs, other osteoporosis medications.

In addition to being poorly compliant in terms of not taking sufficient medication, many patients are not compliant with the strict guidelines associated with current bisphosphonates. In a questionnaire study of 219 patients taking daily risedronate at an osteoporotic clinic, 25% of patients did not comply with dosing instructions, despite receiving counseling [49]. Moreover, 19% of patients discontinued treatment because of adverse events. The most frequently cited adverse events were those of the upper gastrointestinal tract.

In a telephone interview survey of 812 women receiving daily alendronate, a high rate of noncompliance with

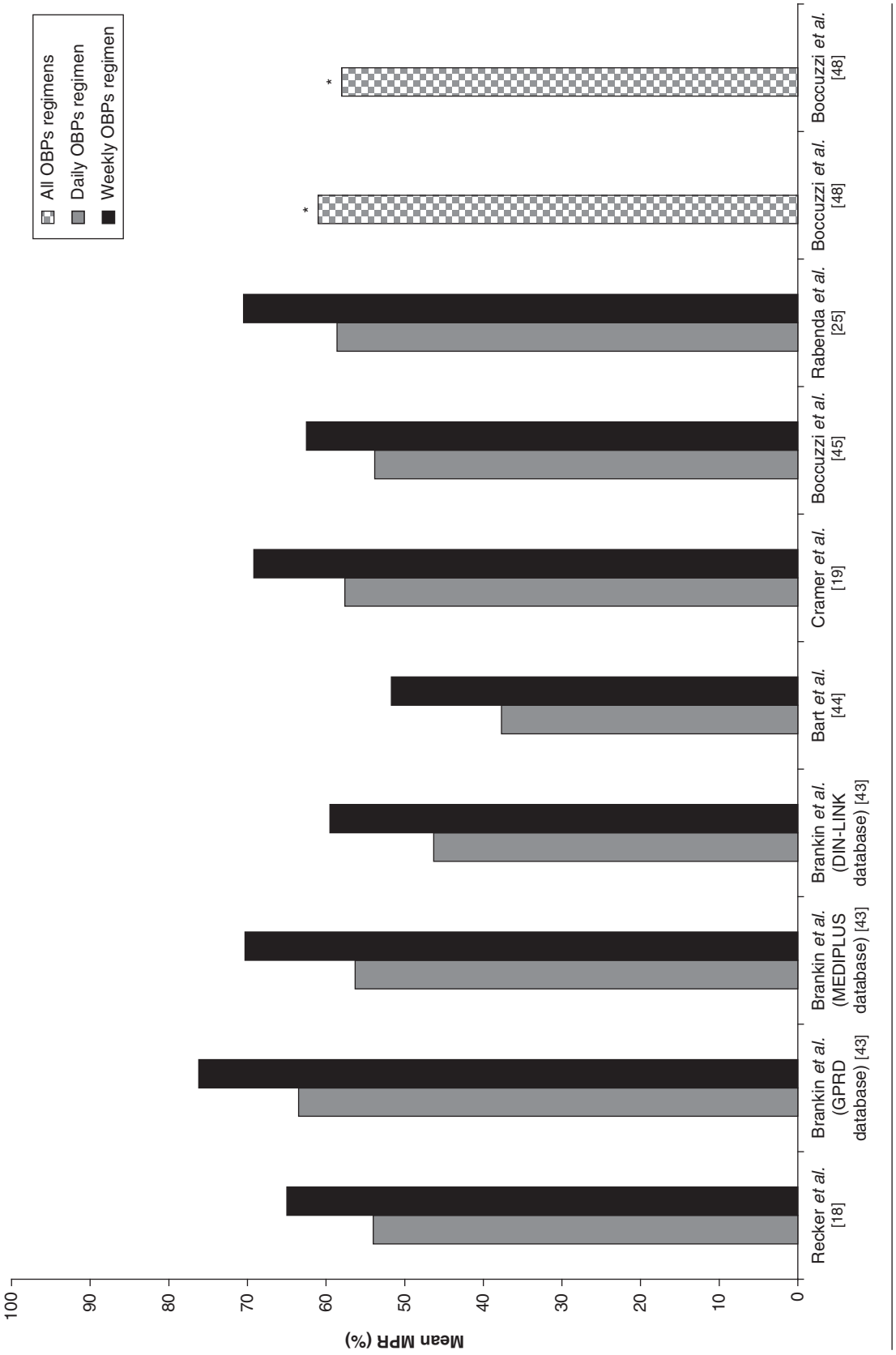

Figure 1. Compliance (mean medication possession ratio) to oral bisphosphonates at 12 months.

*In the Boccuzzi *et al.* study, the reported mean MPR were for alendronate (61%) and for risedronate(58%).

DIN-LINK: Doctors independent network database; GPRD: General practice research database; MEDIPLUS: IMS disease analyzer; MPR: Medication possession ratio; OBP: Oral bisphosphonates.

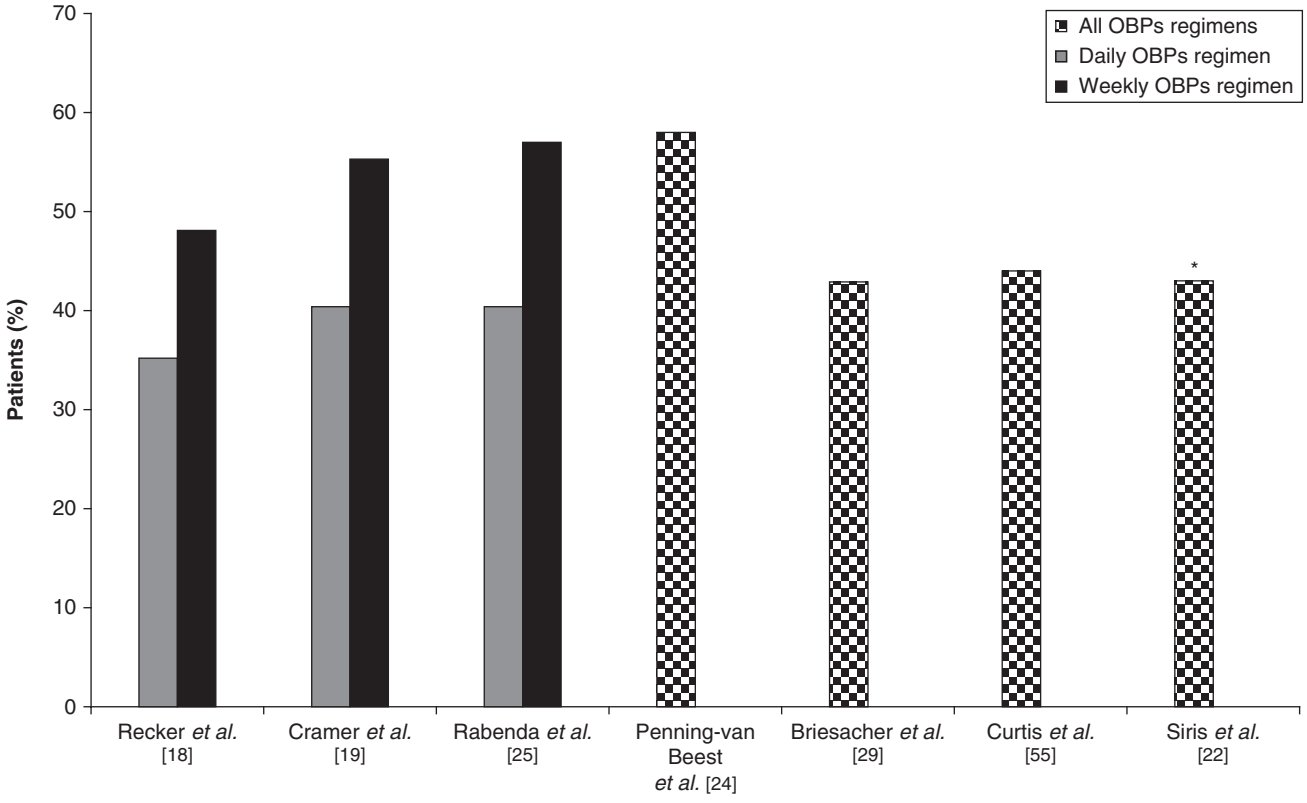

Figure 2. Proportion of patients with adequate compliance (MPR ≥ 80%) at 12 months.
*Proportion of patients with adequate compliance (MPR ≥ 80%) at 24 months.
MPR: Medication possession ratio; OBP: Oral bisphosphonates.

instructions (56%) was reported [50]. In a similarly designed study, Aki *et al.* reported that 12 – 18% patients taking alendronate admitted noncompliance with at least one safety rule and/or absorption rule [51].

3.2 Consequences of poor adherence

3.2.1 Impact of poor adherence on bone turnover markers and bone mineral density outcomes

High adherence to OBP therapy is directly and significantly correlated with an increase in hip and spine BMD and to greater reductions of bone resorption markers in women with low bone mass.

Yood and colleagues studied the effect of compliance on changes in BMD in previously untreated women with osteoporosis [26]. After 1 year of therapy, 70.7% of patients who were prescribed estrogen and 69.2% of patients who were prescribed OBPs continued to take their treatment. Among women whose compliance with therapy was ≥ 66%, the mean increase in spine and hip BMD was 3.8% and 2.6% per year, compared with 2.1% and 2.3% per year for patients whose compliance was < 66% ($p < 0.006$).

Similarly, in a study conducted by Sebaldt and colleagues, patients who reported that they consistently took their prescribed OBPs (≥ 80% of the time) experienced a significant increase in lumbar spine BMD from baseline after 1, 2 and 3 years of therapy (3.3%, 4.9% and 6.5%, respectively) [27]. There was a trend towards a 27% greater 10-year fracture risk in patients who were inconsistent users compared with consistent users. It should be noted that these results are based on self-report and may overestimate consistent use.

In a study by Eastell and colleagues, bone turnover marker levels were measured in 2302 postmenopausal women with osteoporosis, and compliance with OBP treatment was assessed using electronic monitoring [28]. After 22 weeks of therapy, a decrease of ≥ 50% in levels of sCTX from baseline was observed in > 60% of compliant patients versus only 20% of noncompliant patients.

3.2.2 Impact of poor adherence on risk of fractures

McCombs and colleagues were, with Caro *et al.*, one of the first to investigate the relationship between adherence and fracture risk [33]. McCombs *et al.* identified more than 58,000 patients from a large health insurance database in California who 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 (alendronate 245 days, raloxifene 221 days, estrogen 262 days). Persistence significantly reduced the risk of hip (OR = 0.382, $p < 0.01$) and vertebral fractures (OR = 0.601, $p < 0.05$) compared with nonpersistent

patients. The authors also reported that patients who achieved high compliance (360 days of continuous therapy) had a small but significant reduction in physician costs (-$56), hospital outpatient services (-$38) and hospital care (-$155), compared with a $266 increase in prescription drug costs.

In a US health insurance claims database study involving 4769 women, only 24% and 16% were persistent (refill gap ≤ 30 days) with weekly or daily alendronate, respectively [52]. Persistent patients (both weekly and daily alendronate) were 26% less likely to sustain a fracture than the nonpersistent patients (HR = 0.74, 95% CI 0.549 – 0.996; $p < 0.05$).

In a Dutch study using data retrieved from the PHARMO Record linkage system, conducted among 14,4760 women prescribed alendronate (daily or weekly), risedronate (daily or weekly) or etidronate (daily), 43.6% of patients were persistent with treatment at 1 year, decreasing to 27.4% after 2 years of treatment [23]. Van den Boogaard *et al.* performed a nested case control study to evaluate the relationship between persistence OBP use and the risk of hospitalization for osteoporotic fractures. The level of persistence with OBPs in the case group was compared with controls. One year's persistent use of OBPs was associated with a 26% lowered risk of fracture (OR = 0.74, 95% CI 0.57 – 0.95; $p < 0.05$) and two years' persistent use was associated with a 32% lowered risk (OR = 0.68, 95% CI 0.47 – 096; $p < 0.05$).

In another study using the same database as van den Boogaard *et al.*, conducted among 8,845 women prescribing alendronate, risedronate or etidronate, the risk of fracture was reduced by 30% (RR = 0.70, 95% CI 0.50 – 0.99) among patients with at least 1 year of persistent use [53].

Caro and colleagues analyzed a health service database from Saskatchewan, Canada, where over 99% of residents are covered by a health insurance plan [54]. At the end of 2 years of follow-up, less than half of the patients (49.4%) were 'highly compliant' (MPR ≥ 80%) and about 40% had stopped taking medication by the end of follow-up. In this study, compliant patients (MPR ≥ 80%) experienced a 16% lower fracture rate compared with noncompliant patients (HR = 0.84, $p < 0.001$).

Huybrechts *et al.* assessed compliance (defined as MPR ≥ 90%) and persistence in women prescribed HRT or weekly or daily alendronate, using data from a US-managed healthcare database [34]. The follow-up period of this study captures the introduction of weekly bisphosphonates. The average length of follow-up was 1.7 years. At the end of the study, only 26% of women were considered 'good compliant'. Nonpersistence increases gradually over time, reaching close to 22% after 1 year and 45% of the population after 5 years. Poor compliance (defined as MPR ≤ 50%) was associated with a 16.7% ($p < 0.0001$) higher fracture risk during a mean of 1.7 years of follow-up. Compared with ≥ 90% compliance, fracture risk was higher as compliance diminished: 9.1% for 80 – 90% compliance ($p = 0.125$), 18.3% for 50 – 80% compliance ($p = 0.0002$) and 21% for < 50% compliance ($p < 0.0001$). Low compliance (< 80% MPR) with osteoporosis therapy was associated with a $260 increase in monthly medical services.

In another database study, a nested case control design was used to compare the level of compliance with medication in women who had experienced a fracture versus those who had not [21]. In this study, in which about 70% of women were receiving either alendronate or risedronate, a threshold of 90% for the MPR was used to identify 'good compliant' patients. An MPR ≥ 90% was reported in 25.8% of patients with fractures and 33.2% of patients without fractures. The mean MPR was 56% and 60%, respectively. There was an overall lower risk of fracture in those with an MPR ≥ 90% compared with those with an MPR < 30% (OR = 0.72, 95% CI 0.54 – 0.95, $p = 0.019$).

In a cohort of 8822 new users of alendronate or risedronate, Penning-van Beest *et al.* showed that the percentage of patients with an MPR < 80% increased from 34% after 6 months of follow-up to 42% after 1 year, 51% after 2 years and 60% after 3 years of follow-up [24]. When they subdivided MPR in classes, the majority of patients had an MPR of either ≥ 90% or < 20%, with the first group decreasing and the latter group increasing over time. It is important to note that in this study only fractures resulting in hospitalization were considered. They observed a 20% increase in the risk for fracture in individuals with an MPR of 50 – 89%, compared with patients with an MPR ≥ 90% ($p < 0.05$). For patients with an MPR < 20%, an 80% increase in fracture risk was observed compared with compliant patients (MPR ≥ 90%; $p < 0.05$).

In a retrospective cohort study using pharmacy and medical claims data from 45 large US employers, Briesacher *et al.* reported that, after 1 – 3 years of follow-up, only 30.6 – 42.9% of patients could achieve high compliance (≥ 80%) and 33.8 – 52% had very low compliance (< 40%) [29]. The authors showed that patients who were most compliant (≥ 80%) with OBPs had a reduced likelihood of having an osteoporotic fracture in the following year (OR = 0.75, $p < 0.10$) relative to those with the lowest compliance level (< 20%). Moreover, they showed that once compliance fell below 60%, the risk of fracture became no different than for patients with the lowest compliance level (< 20%). They also demonstrated that patients who were most compliant (80 – 100%) with OBPs spent $384 more ($p < 0.05$) on prescription drugs compared with the least compliant (0 – 19%), but $883 (NS) less on inpatient costs and $774 less ($p < 0.05$) on outpatient costs. This resulted in an overall decrease of $1273 ($p < 0.05$) in annual healthcare costs for the most compliant patients relative to the least compliant.

In a large cohort study involving 101,038 new OBP users, Curtis *et al.* reported that only 44% of patients were compliant (MPR ≥ 80%) at the end of the first of year of follow-up [55]. This proportion declined to 39% and 35% at years 2 and 3, respectively. Moreover, patients initially prescribed weekly OBPs had higher MPR at 12 months than those initially prescribed daily OBPs (mean MPR = 45% vs 38%, $p < 0.001$). They

evaluated the rate of fracture among noncompliant patients (MPR < 50%) compared with highly compliant patients (MPR ≥ 80%) across several age strata and a variety of types of clinical fracture. The largest significant hazard ratio for any age group and fracture type was for hip fractures among 65 – 78-year-olds, where noncompliant patients were observed to have an adjusted 1.74-fold greater risk (95% CI 1.30 – 2.31) for fracture. For all non-hip, non-spine fractures, there was an approximately 10 – 30% elevation in fracture rates for the noncompliant compared with the compliant patients, depending on age group.

In a study using data from the Ontario Medicare database and including 74,085 patients receiving OBPs or selective estrogen receptor modulators (SERMs), Jaglal *et al*. estimated the impact of compliance on the risk of fracture, using different MPR cutoffs (30, 50, 67 and 80%) [56]. MPRs of > 67% and > 80% were associated with a reduction in fractures (OR = 0.85, p < 0.05).

Only five studies investigated the impact of both persistence and compliance on fractures risk. Siris *et al*. examined claims data from two large pharmaceutical databases [22]. Among 35,537 women initiating OBP treatment, 43% were refill compliant (MPR ≥ 80%) and only 20% persisted with treatment after 2 years. In addition to persistence and compliance, the Siris study also examined the effect of both persistence and compliance on fracture rate. Persistence was associated with a 29% reduction in the risk of nonvertebral fractures and a 44% reduction in the risk of hip fractures alone (p < 0.001). Women who achieved compliance with therapy had a 21% (p < 0.001) reduction in fractures overall compared with those who were not compliant. The greatest risk reduction was for hip fractures (37%, p < 0.001). In addition, they examined fracture probability as a function of the MPR. The risk of fracture remained largely unchanged for MPR values of up to approximately 50%, declining with a shallow slope for MPR values between 50% and 75% and then more sharply between 75% and 100%.

In the second study examining both persistence and compliance with OBP treatment and its impact on fracture risk, we conducted a retrospective cohort analysis of data from the Belgian national security database [25]. Among women initiating OBP treatment, the mean MPR at 12 months was 64.7% and was significantly higher for patients receiving weekly alendronate compared with those who received daily alendronate (70.5% vs 58.6%, p < 0.001). The rate of persistence (using a refill gap ≥ 35 days) at 12 months was 39.5% and decreased over time. They found that for each 1% reduction in MPR, the risk of hip fracture increased by 0.4%. The relative risk reduction for hip fracture was 60% for persistent patients compared with nonpersistent patients (HR = 0.4, 95% CI 0.357 – 0.457; p < 0.0001).

In another study including 4451 users of OBPs, high compliance reduced the fracture risk by 39% (HR = 0.61, 95% CI 0.47 – 0.78; p < 0.01) compared with low compliance (MPR < 80%) [57]. In subjects with a previous fracture, uninterrupted OBP therapy reduced fracture rates by 29% over 180 days (p = 0.025), 45% over 1 year (p = 0.001) and by 9% over 2 years (p = 0.001).

In a retrospective case-control analysis of data derived from the Thales prescription database, the mean MPR was significantly lower in cases (i.e., patients who sustained an osteoporotic-related fracture during the follow-up) compared with controls (58.8% vs 72.1%, p < 0.001) [58]. Cases were also more likely to discontinue osteoporosis treatment than controls (50% vs 25.3%, p < 0.001), yielding a significantly lower proportion of patients who were persistent at 1 year (34.1% vs 40.9%, p < 0.001). Women who achieved an MPR threshold ≥68% had a 51% reduction in fracture risk, compared with less compliant patients (OR = 0.49, 95% CI 0.39 – 0.61; p < 0.01). The authors evaluated that the optimal threshold for persistence with therapy was at least 6 months. Attaining this threshold was associated with a 28% reduction in fracture risk, compared with less persistent women (OR = 0.72, 95% CI 0.57 – 0.90; p < 0.01).

In a retrospective cohort study using data from a claims database of a German statutory sickness fund, Hoër *et al*. estimated compliance (MPR ≥ 80%) at 6 months, 1 year and 2 years among patients with and without a previous fracture [59]. Among patients without a previous fracture, proportions of compliant patients were 55.6%, 43.2%, 29.7%, at 6 months, 1 year and 2 years, respectively. In patients with a previous fracture, rates of compliant patients were slightly higher (61.6%, 49.3%, 42.1%). Fracture rates were reduced by 29% (p = 0.025) among persistent patients with a previous fracture within 180 days after the index prescription and by 45% (p < 0.001) within 360 days. Good compliance (MPR ≥ 80%) reduced the fracture risk by 39% in all patients (HR = 0.61, 95% CI 0.47 – 0.78; p < 0.01). The fracture risk was significantly increased in patients with previous fracture (HR = 10.32, 95% CI 8.09 – 13.16; p < 0.001).

4. Conclusion

In conclusion, there is strong evidence that compliance and persistence with OBPs are poor and suboptimal in clinical practice. The extension of dosing intervals between daily and weekly have enhanced adherence, but these improvements are marginal. Less frequent regimens such as once-monthly, once-quarterly or once-yearly administration may increase patient convenience and therefore potentially improve compliance and achieve the full potential benefit of bisphosphonate therapy. Most importantly, poor adherence to osteoporosis medications has been shown to be associated with a significantly greater risk of fractures.

Despite these facts, there should be substantial hope that these behaviors can be changed in the future. It is essential that physicians be encouraged to take measures to increase patients' awareness of the need to use osteoporosis medications as directed in order to gain their full benefit. It is important

for patients to note that even small departures from full adherence are associated with higher risks of fracture and, consequently, with substantial costs for the community.

5. Expert opinion

The studies included in this review evaluated persistence and compliance with OBPs in clinical practice, using a variety of sources and patient populations. Overall, the data consistently demonstrated that both compliance and persistence levels with OBPs, in clinical practice, are poor and suboptimal, with many patients discontinuing treatment soon after therapy initiation. The studies that assessed the consequences of poor compliance and persistence constantly demonstrated an increased risk of fracture in patients who did not follow their dosing regimens [21-25,29,33,34,53-60]. Additionally, some of them showed that low rates of adherence contribute to increased healthcare expenditure [29,33,34].

Differences in methodology and in patient demographics resulted in wide variations in persistence and compliance reported rates. Most of the studies measured persistence as a function of the gap between refills, by identifying the percentage of patients who do not refill their medication within a given grace period and measuring timeliness and continuity of medication use. Few studies analyzed the effect of varying refill gap lengths on persistence rates, finding that higher persistence rates were obtained with longer refill gaps [20,25]. In two studies, it was shown that many patients restarted osteoporosis therapy after a prolonged lapse in medication use [20,42]. Although it is encouraging that patients have been reinitiating use of their medications, the effect of these long breaks on clinical outcomes is unknown. The protective therapeutic time window following a stop or interruption in treatment needs to be investigated further.

In most of the studies, compliance was measured using the MPR. The methods used to calculate this ratio were similar across studies, although some of them computed it over a period of 365 days, whereas others assessed it at 90-day intervals, which prohibited direct comparisons between studies. Many studies used an MPR of 80% or higher as a clinically relevant threshold or measure of good compliance. In studies evaluating the impact of compliance on the risk of fracture, dichotomizing compliance by using a threshold could compromise results because cutoff points are arbitrary and could lead to loss of information. It does not give information on the point at which there is a significant shift in fracture risk. The 80% cutoff used to define the proportion of ingested medications that indicates satisfactory compliance is not fully agreed on. Moreover, patients considered as noncompliant (i.e., MPR < 80%) are, by definition, a very heterogeneous group as for their levels of compliance. The effects of modest compliance on fracture rates would be different than those of lowest compliance. Use of several compliance categories or of the full range of compliance values may weaken these effects and provide more accurate data. For physicians as well as patients, it is important to establish a clear point below which medication provides no benefit.

As already mentioned, definitions of adherence, persistence or compliance varied across the studies and were used interchangeably in those studies. This variation most likely reflects the multifactorial nature of medication-taking behavior and variation in its reporting. However, the interpretation of these studies is hindered by heterogeneity in the parameters used to evaluate adherence. There is a pressing need to standardize terms and definitions and for conceptual frameworks of adherence that guide research and clinical practice [60].

A great number of the studies assessed either persistence or compliance. Given that adherence is complex, a combination of measures seems warranted to capture fully the various aspects of adherence. Moreover, few studies assessed compliance and persistence rates over longer periods (> 2 years from treatment initiation), indicating that more studies are needed to provide additional information on long-term compliance and persistence with drug therapy for osteoporosis.

Although OBPs are the most potent approved antiresorptive agents at present, this treatment can pose a particular challenge, since these medications require more effort than simply swallowing a pill. Current OBPs need to be administered according to strict treatment guidelines to achieve optimum absorption and minimize the risk of adverse gastrointestinal events. These include the need to remain in an upright position for at least 30 min after administration and before eating breakfast, and to swallow the medication with water only. These strict treatment guidelines can contribute to poor adherence but also decrease the efficacy of treatment if they are not adequately respected. Studies of self-reported drug-taking behavior have shown that, even when complete instructions are given, between 25% and 50% of patients disregard at least one requirement [50-52].

The extension of dosing intervals, most notably for OBPs, generated considerable enthusiasm initially. By limiting the need to comply with these dosing requirements to once a week, such intermittent regimens have increased the likelihood that patients will continue with therapy. However, although statistically significant, the improvements produced by weekly dosing have been modest, about 10%, indicating a need for further compliance-enhancing strategies. Bisphosphonates with less frequent dosing regimens than once weekly have become available, including the once-monthly oral and quarterly intravenous ibandronate formulations, as well as the once-yearly intravenous zoledronate. They have been shown to be well tolerated and effective against osteoporotic fractures, showing similar or superior BMD gains and osteoporotic fractures risk reductions compared with more frequent regimens [61-64]. 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. The results from the PERSIST trial showed that once-monthly ibandronate, coupled with a patient support program, improved persistence on treatment, compared with once-weekly alendronate [47]. Two clinical studies (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 [65,66]. Intermittent intravenous (i.v.) administration has the advantage of less frequent administration and, in addition, avoids the problems of reduced bioavailability and upper gastrointestinal adverse events. They may be particularly useful for patients who experience gastrointestinal adverse events with oral agents or cannot adhere to strict oral dosing requirements. These benefits might promote long-term compliance and so optimize patient management. It has been shown that women who had discontinued daily or weekly oral OBPs because of gastrointestinal intolerance reported decreased gastrointestinal symptoms and improved adherence on quarterly i.v. or monthly oral ibandronate [67]. Eighty-three per cent of quarterly i.v. ibandronate recipients and 70% of monthly oral ibandronate recipients remained adherent at 12 months. In two separate trials, yearly i.v. zoledronate was preferred to weekly oral alendronate by 79% [68] and 66% [69] of patients. However, the impact of these new formulations on persistence and compliance in real-life settings remains to be determined. Moreover, the extension of dosing intervals increases the importance of full compliance with therapy because the therapeutic consequences of missing a monthly or a quarterly dose may be more substantial than with a weekly or daily dose. Simplification of the medication regimen is unlikely to solve completely the problem of nonadherence with bisphosphonates, but should be one component of a multifactorial strategy.

The consequences of poor adherence are serious. As already mentioned, noncompliant patients experience poorer clinical outcomes including a higher risk of fracture. Moreover, poor adherence contributes to increased healthcare expenditure. As demonstrated by a recent modeling study, nonadherence with osteoporosis medications results not only in worsening health outcomes, but also in a significant change in the cost-effectiveness of treatments [70]. In another recent study, the estimated number of osteoporotic fractures that would be avoided among compliant patients (MPR $\geq$ 80%) was 110 in the primary prevention cohort and 19 in the secondary prevention cohort [71]. The cost of these avoidable fractures per patient was $62.90 in primary prevention cohort and $330.80 in secondary prevention cohort. Moreover, analysis of the relationship between mortality in clinical studies and adherence to treatment regardless of indication and diagnosis has proved that good adherence is associated with lower mortality [72].

Given the aging population and the burden of osteoporosis, there has been increasing interest in the development of interventions to promote patient adherence with effective therapeutic regimens. Some studies have suggested that implementing monitoring or giving feedback to patients, such as bone turnover marker or BMD information, as a tool to improve long-term adherence, may result in an improved outcome for patients with postmenopausal osteoporosis [73,74]. However, a recent Cochrane review found that in randomized trials, less than half of interventions designed to improve adherence were associated with statistically significant improvements in medication adherence and less than one-third improved outcomes [75]. Effective interventions involved combinations of several interventions, and it is not known which of them were the most effective.

Improving patient adherence with osteoporosis therapy requires effective patient–provider communication and close monitoring for early identification of declining adherence [76,77]. Poor persistence occurs as early as 3 months of starting treatment, indicating the need for early monitoring. Moreover, it has been showed that patients new to OBPs had the worst compliance [18], suggesting that a close monitoring is imperative at the outset of the treatment.

A patient's preferences or desire for taking a medication is another important consideration in osteoporosis management, as with other diseases. In determining the best therapy for a particular patient, efficacy and tolerability are important considerations. In addition, ease of use and dosing convenience are important features to consider in encouraging long-term compliance to therapy for chronic conditions such as osteoporosis. Although the special requirements for taking OBPs (timing of the dose, fasting etc.) cannot be modified, frequency of dosing could be addressed by offering patients the choice of how often they would prefer to take their medication. These preferences may be based on their lifestyles and needs. Some studies have suggested that patients prefer to extend dosing intervals for their OBP medications [65,66,78,79]. As with any therapeutic decision, physicians must involve the patient and ensure that the specific therapy for each patient is individually tailored to their preferences. This active participation in treatment decisions will probably improve compliance.

In addition to adherence, a continuing challenge in the management of osteoporosis is the underdiagnostic and undertreatment of the disease. Several studies in different countries have observed that a significant proportion of patients did not receive any treatment for osteoporosis even after a fracture [12-15]. Most important, a recent study demonstrated that among the very small proportion of patients treated following a hip fracture (6%), only 41% of women continued to take their treatment at the end of the first year of therapy and less than half were found to be compliant with OBP therapy (MPR $\geq$ 80%) [16]. Healthcare providers should be educated on the need to identify patients with osteoporosis and prescribe osteoporosis medications. Additionally, they need to be conscious of problems with adherence and the need to monitor and support their patients in this important task.

Declaration of interest

JY Reginster has received consultancy fees from/is on the advisory board of Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS and Theramex. He has received lecture fees when speaking at the invitation of a commercial sponsor from Merck Sharpe and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed and Novo-Nordisk. He has received grant support from Bristol Myers Squibb, Merck Sharpe and Dohme, Rottapharm, Teva, Lilly, Novartis, Roche, GlaxoSmithKline, Amgen and Servier. The other authors declare no conflicts of interest.

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