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Potential Clinical and Economic Impact of Nonadherence with Osteoporosis Medications

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Abstract This study aims to estimate the potential clinical and economic implications of therapeutic adherence to bisphosphonate therapy. A validated Markov microsimulation model was used to estimate the impact of varying adherence to bisphosphonate therapy on outcomes (the number of fractures and the quality-adjusted life-years [QALYs]), health-care costs, and the cost-effectiveness of therapy compared with no treatment. Adherence was divided into persistence and compliance, and multiple scenarios were considered for both concepts. Analyses were performed for women aged 65 years with a bone mineral density *T*-score of −2.5. Health outcomes and the cost-effectiveness of therapy improved significantly with increasing compliance and/or persistence. In the case of real-world persistence and with a medical possession ratio (MPR; i.e., the number of doses taken divided by the number of doses prescribed) of 100%, the QALY gain and the number of fractures prevented represented only 48 and 42% of the values estimated assuming full persistence, respectively. These proportions fell to 27 and 23% with an MPR value of 80%. The costs per QALY gained, for branded bisphosphonates (and generic alendronate), were estimated at €19,069 (€4,871), €32,278 (€11,985), and €64,052 (€30,181) for MPR values of 100, 80, and 60%, respectively, assuming real-world persistence. These values were €16,997 (€2,215), €24,401 (€6,179), and €51,750 (€20,569), respectively, assuming full persistence. In conclusion, poor compliance and failure to persist with osteoporosis medications results not only in deteriorating health outcomes, but also in a decreased cost-effectiveness of drug therapy. Adherence therefore remains an important challenge for health-care professionals treating osteoporosis.

Keywords Adherence · Burden · Compliance · Cost-effectiveness · Osteoporosis · Persistence

Poor compliance and failure to persist with drug therapy are common in chronic diseases [1], especially in asymptomatic diseases where treatment benefit is not immediately perceived by the patient. Nonadherence limits the potential benefits of drug therapy and is of potential clinical and economic significance [2–4]. Osteoporosis is typically a chronic asymptomatic disease which requires long-term treatment. Patient adherence to treatments for osteoporosis remains poor and suboptimal in clinical practice [5–7]. Numerous studies conclude that approximately 50–75% of women who initiate antiosteoporosis drug therapy discontinue treatment before the end of the first year [6, 8]. Poor adherence has been shown to lead to a significant increased risk of vertebral and nonvertebral fractures [6, 7]. Therefore, the clinical and economic implications of nonadherence are potentially significant but have not been well documented.

This study aims to evaluate the potential clinical and economic implications of nonadherence to bisphosphonate therapy. More specifically, it assesses the impact of varying medication compliance and persistence on outcomes (number of fractures and quality-adjusted life-years [QALYs]), total and disaggregated health-care costs, and cost-effectiveness of osteoporosis medications. Analyses were performed in Belgian women aged 65 years at the

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threshold for osteoporosis (i.e., bone mineral density *T*-score of −2.5 [9]), using a validated Markov microsimulation model.

Methods

Definition of Medication Adherence

In the literature, there is a wide variety of definitions of medication adherence [3]. Recently, the International Society for Pharmacoeconomics & Outcomes Research set out definitions [10]. Medication adherence is a general term, encompassing two different constructs, i.e., persistence and compliance. Medication compliance may be defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [10]. It is typically expressed as the number of doses taken divided by the number of doses prescribed, often called the medical possession ratio (MPR) [10]. Medication persistence is defined as "the duration of time from initiation to discontinuation of therapy" [10]. It may be reported as the proportions of patients receiving therapy at different time periods.

Economic Model

A validated Markov microsimulation model was used to estimate the impact of medication adherence on outcomes, health-care costs, and the cost-effectiveness of oral bisphosphonates compared with no treatment. The model health states were no fracture, hip fracture, clinical vertebral fracture, forearm fracture, other fractures, and death. The cycle length of the model was set to 1 year and all patients were followed until the age of 105 years or death. Beginning in the no-fracture state, each patient had a probability of having a fracture, remaining healthy, or dying in every year, regardless of his or her current state. Each state had its associated costs and outcomes, depending on the patient history.

The analysis was performed from a health-care perspective, including direct health-care costs paid by national health insurance and the individual patient's out-of-pocket contribution [11]. Total health-care costs were disaggregated into drug-related costs (i.e., drug and monitoring costs) and disease cost, which included direct fracture costs in the year following the fracture and long-term costs beyond the first year after a hip fracture. Outcomes were measured as the number of fractures and QALYs. In accordance with Belgian methodological guidelines for pharmacoeconomic evaluations [11], discount rates of 3 and 1.5% were assumed in the base-case analysis for costs (expressed as €) and QALYs, respectively. All model parameters were selected from the Belgian literature, the country of reference for the present analysis, wherever possible, and from systematic literature reviews otherwise.

The incidence of first fracture was estimated in a previous study [12]. The risk of hip fracture was based on a Belgian epidemiologic study [13], and the risk of other fractures was imputed using fracture rates from other countries, assuming a similar ratio between hip and other fractures between countries [14]. This assumption appears to be reasonable and consistent for West Europe, the United States, and Australia [15–18]. Mortality rates were obtained from an official source [19], and excess mortality was assumed after a hip and clinical vertebral fracture. The excess mortality was derived from a Swedish-based population study [20] and decreased in subsequent years for both types of fracture. Because excess mortality may also be attributable to comorbidities, only 25% of the excess mortality was conservatively assumed to be attributable to the fractures [21, 22].

Cost estimates are expressed as €2006 and were adjusted by consumer price indexes when necessary. Direct hip fracture cost, including the cost of hospitalization and the extra costs in the year following the fracture, ranged from €16,579 to €20,306 [23, 24]. Forearm fracture cost was estimated at €2,159 [25]. The costs of clinical vertebral and other fracture were quantified relative to hip fracture cost. Assuming that these represent 17 and 25%, of hip fracture cost [26, 27], respectively, they were estimated at €2,429 and €3,573. Hip fracture costs for the subsequent years were based on the proportion of patients being institutionalized following the fracture, ranging from 5 to 30% [23]. Nonhip fractures were assumed not to be associated with long-term costs.

Utility values for the general population as well as relative reductions due to fractures were derived from a recent systematic review [28]. From this study, the proportional loss in QALY in the year following a hip, clinical vertebral, wrist, or other fracture were 0.20, 0.28, 0.06, and 0.09, respectively [28]. The QALY loss related to hip and clinical vertebral fracture in the second and following years were 0.10 and 0.07 [28]. Wrist and other fractures were not associated with a QALY reduction in the long-term. In case of the occurrence of a second fracture at the same site, we reduced by 50% the disability allocated to the first fracture event [29]. A more detailed description and explanation of the model and data have been published elsewhere [29].

The base-case analysis was performed for women aged 65 years with a bone mineral density (BMD) *T*-score of −2.5, the threshold for the operational definition of osteoporosis [9], and no prior fracture. The risk of first fracture in the general population [12] was adjusted to reflect the increased fracture risk of these women compared to that of the general population, using a previously described and

validated method [30, 31]. The estimated relative risks for women aged 65 years at the threshold for osteoporosis were 1.705, 1.545, 1.338, and 1.456 for hip, clinical vertebral, wrist, and other fractures, respectively.

Bisphosphonate Therapy

Treated women were assumed to be receiving bisphosphonate therapy, the most widely prescribed antiosteoporosis drug class worldwide. In order to assess the cost-effectiveness of osteoporosis medications, data were required on fracture risk reduction (at specific sites), treatment duration, effect of treatment after stopping therapy, treatment cost, treatment-related adverse events, and medication adherence [29] (Table 1).

A recent meta-analysis conducted for the National Institute for Health and Clinical Excellence appraisal investigated the clinical effectiveness of oral bisphosphonate therapies (pooled data from alendronate and risedronate) in the treatment of women with osteoporosis [32]. Oral bisphosphonate was shown to significantly reduce the risk of hip fracture, by 29% (relative risk, 0.71; 95% CI, 0.58–0.87), compared with placebo; the risk of clinical vertebral fracture, by 42% (relative risk, 0.58; 95% CI, 0.51–0.67); and the risk of wrist and other fractures, by 22% (relative risk, 0.78; 95% CI, 0.69–0.88). Patients were assumed to be treated for a maximum of 3 years, as in the clinical trials, and the effect of treatment was assumed to decline linearly after stopping therapy for a period (i.e., 'offset time') equal to the duration of therapy, in accordance with clinical studies [33, 34] and previous cost-effectiveness analyses [35].

In the base-case analysis, we assumed the average cost of the two bisphosphonates (branded price), i.e., alendronate (Fosamax; €70.94 for a package of 12 70-mg tablets, once per week [36]) and risedronate (Actonel; €97.19 for a package of 12 70-mg tablets, once per week [36]). The annual cost was therefore estimated in Belgium at €365.28. In addition to the drug cost and in line with previous assumptions about monitoring of osteoporotic treatments [35], we also assigned the cost of a yearly doctor's appointment (€20) for patients receiving therapy and the cost of a BMD measurement at years 1 and 3 (€47). No adverse events were included in the base-case analysis since the overall safety profile of bisphosphonates is favorable [37].

Medication Persistence and Compliance

Persistence and compliance to bisphosphonate therapies (daily and weekly combined) were derived from a large observational Belgian study [6], the reference country for the analysis. Two scenarios were investigated for medication persistence, including real-world persistence and full persistence over 3 years. Real-world persistence assumed that approximately 30, 12, 18, and 15% discontinued therapy at 3 months, 6 months, 1 year, and 2 years of therapy, respectively [6]. Patients who switched from daily to weekly oral bisphosphonates were considered persistent in the observational study [6]. If patients discontinued therapy at 3 months, they were assumed to receive no treatment effect; however, 3 months of drug costs and monitoring costs was incurred. Offset time for nonpersistent patients was the same as the treatment period and patients who discontinued therapy were assumed to receive no further treatment.

Medication compliance was quantified as MPR, which is defined as the number of days of medication supply received divided by the 365 potential days of supply [38], and ranged from 10 to 100%. The relative risk of fracture during therapy was dependent on the MPR value and the drug cost was assumed to be proportional to the MPR value. It was assumed that the effectiveness of oral bisphosphonates in the meta-analysis was applicable to the population with an MPR value of 80%. Fracture reduction efficacy at other MPR values was estimated based on the relationship between compliance and fracture risk. For hip fracture, a linear reduction between MPR value and probability of hip fracture was suggested by the Belgian study [6], which considered MPR to be a time-dependent variable. The relationship between compliance and nonhip fracture, not investigated in the Belgian study, was derived from a large U.S. study including 35,537 patients who received a bisphosphonate prescription [7]. In this study

Table 1 Assumptions on bisphosphonate therapy

Annual therapy cost	€365.28 [36]
Maximum duration of therapy	3 years
Offset time	Linear decrease in fracture risk reduction for a period equal to the duration of therapy [33, 34]
Persistence	70, 58, 40, and 25% of patients persistent at 3 mo, 6 mo, 1 year, and 2 years of therapy [6]
	No treatment effect for patients who discontinued therapy in the first 3 mo
Adverse events	€0 [37]

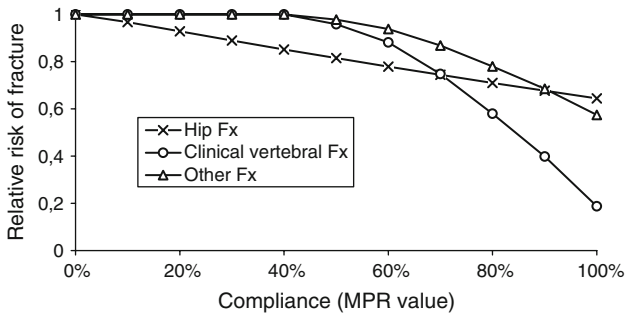

Fig. 1 Relative risks of fracture (Fx) with bisphosphonate therapy at the sites shown, according to compliance. Assumptions built into the model. With a medical possession ratio value of 80%, the relative risks of hip, clinical vertebral, and other fractures were 0.71, 0.58, and 0.78, respectively. The equivalent values were 0.64, 0.19, and 0.57 with an MPR of 100%, and 0.78, 0.88, and 0.94 with an MPR of 60%

assessing the relationship between MPR and any fracture, the probability of fracture remains largely unchanged for repeat prescription compliance values up to approximately 0.50 [7]. The probability then declines slightly for MPR values from 0.50 to 0.75 and more sharply from 0.75 to 1 [7]. Figure 1 summarizes the relative risks of fracture built into the model for bisphosphonate therapy, according to compliance (i.e., MPR value) and fracture type.

Analyses

Monte Carlo microsimulations were performed for each scenario, and outcomes (number of fractures and QALYs) and health-care costs (drug-related and disease costs) were recorded. A total of 200,000 trials was sufficient to ensure high stability of the cost-effectiveness results. The model was constructed using TreeAge Pro 2006 (TreeAge Software Inc., Williamston, MA, USA).

As a primary analysis, the incremental cost-effectiveness ratio (ICER), expressed as cost per QALY gained, was estimated for each adherence scenario compared with no treatment. Sensitivity analyses were performed for four specific adherence scenarios including full adherence (i.e., full persistence and MPR value of 100%) and real-world persistence, with MPR values of 100, 80, and 60%. One-way sensitivity analyses were used to assess the impact of a single parameter on the results and were conducted on discount rates, fracture cost, fracture risk, fracture disutility, age at start of treatment, fracture reduction benefit, and therapy cost, including the cost of generic alendronate (i.e., Beenos; €37.8 for a package of 12 70-mg tablets, once per week [36]). Additional simulations assessed the impact of the relationship between compliance and fracture risk on the changes in ICER in the case of changes in compliance. Probabilistic sensitivity analyses were also performed to examine the effect of the joint uncertainty surrounding nearly all model parameters. A description of the data distribution used has been published elsewhere [29]. In addition, the effect of treatment on fracture risk was assumed to be log-normally distributed, as suggested for relative risk parameters [39]. Cost-effectiveness acceptability curves were constructed from the incremental cost and effectiveness for 150 simulations. They show the probability of being cost-effective over a range of willingness to pay per QALY gained.

Results

Figure 2 illustrates the impact of medication compliance and persistence on outcomes (number of lifetime fractures per patient and QALYs). The QALY gain and the number of fractures prevented with drug therapy improved

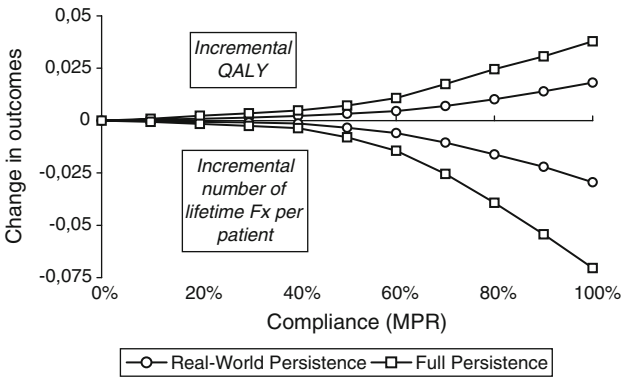

Fig. 2 Impact of medication compliance and persistence on outcomes expressed as quality-adjusted life-years (QALY) and on the number of lifetime fractures per patient. *MPR* medical possession ratio

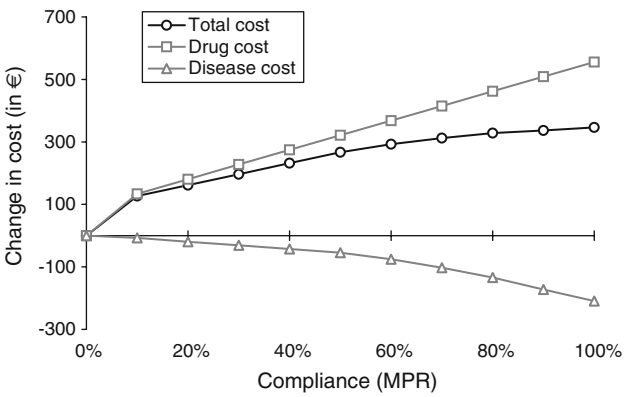

Fig. 3 Impact of medication compliance on total and disaggregated (drug and disease) costs, assuming real-world persistence**.** MPR, medical possession ratio

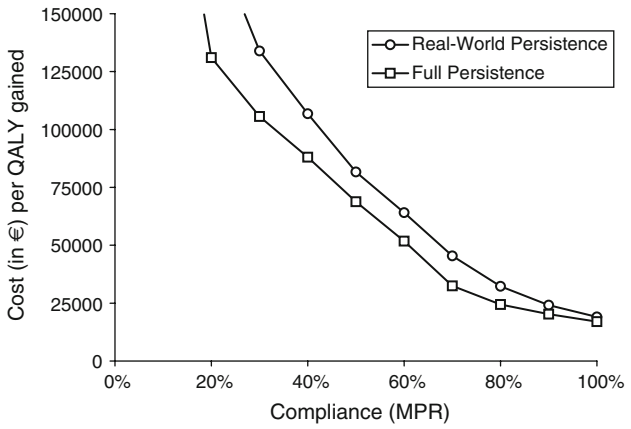

Fig. 4 Impact of medication compliance and persistence on the cost-effectiveness of branded bisphosphonates compared with no treatment. *MPR* medical possession ratio; *QALY* quality-adjusted life-years

significantly with increasing compliance and/or persistence. In the scenario using real-world persistence and an MPR value of 100%, the QALY gain and the number of fractures prevented represented only 48 and 42% of the estimated values, assuming full adherence (full persistence and an MPR value of 100%), i.e., the best-case scenario. With an MPR value of 80%, these proportions fall to 27 and 23%, respectively.

Figure 3 presents the relationship between compliance and the changes in total health-care costs and disaggregated costs (drug and disease costs), using real-world persistence rates. Total health-care costs were shown to increase with compliance, as the cost of the additional therapy stemming from the improved compliance always exceeded the averted costs of treating the additional osteoporotic fractures resulting from noncompliance.

Table 2 Univariate sensitivity analyses on the impact of medication adherence on the cost-effectiveness of bisphosphonate therapy

Parameter	Full Pe. MPR, 100%	RW Pe. MPR, 100%	RW Pe. MPR, 80%	RW Pe. MPR, 60%
Base case	16,997	19,069	32,278	64,052
Model parameters				
Discount rate				
3%	22,125	26,067	34,254	67,495
5%	33,217	40,055	66,178	84,879
BC fracture costs				
0.75 time	21,084	27,839	38,414	70,509
1.25 time	11,961	16,563	24,925	57,453
BC fracture risk				
0.75 time	30,188	39,100	56,240	107,855
1.25 time	11,724	13,736	20,091	47,717
BC fracture disutility				
0.75 time	22,126	26,927	34,272	67,807
1.25 time	16,458	18,457	30,792	53,287
Age at start of treatment				
60 years	24,351	31,970	44,025	73,634
70 years	11,910	14,280	21,063	36,760
Treatment				
Treatment cost				
20% higher	22,366	24,227	39,651	76,356
20% lower	11,628	13,911	24,905	51,748
Alendronate cost				
Brand-name	12,805	15,042	26,522	54,446
Generic	2,215	4,871	11,985	30,181
Treatment efficacy				
20% higher	12,851	15,608	25,582	49,746
20% lower	23,883	26,422	40,288	74,593
Adherence				
Relationship between compliance & fracture risk reduction risk reduction				
Linear	27,331	37,005	39,291	42,600
Nonlinear	12,471	15,206	40,184	100,541
Meta-analysis efficacy valuescorrespond to an MPR of 100%	34,319	45,822	58,628	79,092
RW Pe. 50% higher	–	17,923	25,461	56,918

BC base case, *MPR* medical possession ratio, *Pe.* persistence, *RW* real-world

The cost-effectiveness of branded bisphosphonates compared with no treatment is presented in Fig. 4, for different compliance and persistence scenarios. The figure shows that cost-effectiveness improved with increasing compliance and/or persistence. Compliance had a more marked effect than persistence. The costs per QALY gained, for branded bisphosphonate (and generic alendronate), were estimated at €19,069 (€4,871), €32,278 (€11,985), and €64,052 (€30,181), respectively, with MPR values of 100, 80, and 60%, in the case of real-world persistence. These values were €16,997 (€2,215), €24,401 (€6,179), and €51,750 (€20,569) when assuming full persistence.

The cost-effectiveness of four adherence scenarios was assessed for one-way sensitivity analyses (Table 2). Although model parameters and treatment specificities had an impact on the cost per QALY gained of drug therapy, they did not significantly influence the relative importance of the alternative scenarios. Cost-effectiveness always improved with increasing compliance and/or persistence. The relationship between compliance and fracture risk reduction had a marked effect on the impact of medication compliance on cost-effectiveness. When assuming a linear relationship for any fractures, as observed in the Belgian study [6] for hip fracture, compliance had only a modest impact on the cost-effectiveness of bisphosphonate treatment, while compliance had a large impact when assuming a nonlinear reduction for any fractures, in concordance with the study by Siris et al. [7].

Probabilistic sensitivity analyses showed that the probability of oral bisphosphonates being cost-effective increased significantly with both improving compliance and persistence (Fig. 5). For example, at an assumed willingness to pay of €40,000 per QALY gained, these probabilities were, for branded bisphosphonates and (generic) alendronate, 99.3% (100.0%), 95.3% (99.3%), 64.0% (97.3%), and 12.0% (74.7%), respectively, for the different scenarios.

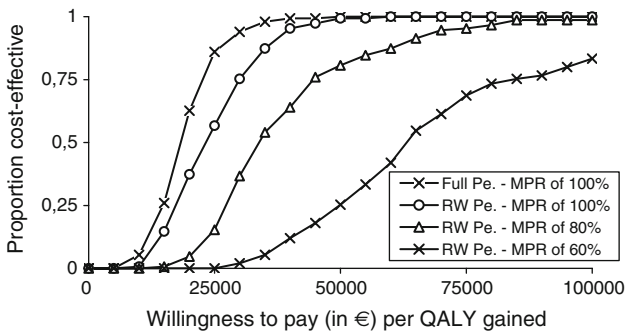

Fig. 5 Impact of medication adherence on the cost-effectiveness acceptability curves of branded bisphosphonates. *MPR* medical possession ratio, *Pe* persistence, *QALY* quality-adjusted life-years, *RW* real-world

Discussion

Poor adherence to osteoporosis medication reduces the drug's potential effectiveness and results in decreasing health outcomes and worsening the cost-effectiveness of drug therapy. This study examined the potential clinical and economic consequences of nonadherence with oral bisphosphonates, by mixing and testing different scenarios for both compliance and persistence.

Poor compliance and failure to persist with oral bisphosphonates may substantially reduce their potential clinical benefits. Assuming real-world persistence and MPR values of 100% and of 80%, the number of fractures prevented represented only 42 and 23% of the values obtained assuming full adherence (full persistence and MPR value of 100%), respectively. Although such a population does not exist in real life, the potential benefits of oral bisphosphonates in terms of number of fractures prevented, as well as QALY gain, would be reduced by between 50 and 75% through poor adherence.

Because higher adherence also increased health-care costs, it is important to assess the impact of adherence on the cost-effectiveness of drug therapy. Our results suggest that compliance and persistence have a significant impact on the ICER of oral bisphosphonates. In the case of assumed real-life persistence assumption, the cost per QALY gained doubled when the MPR decreased from 80 to 60%. The benefits of increased persistence were, however, less marked and were neutralized, to some extent, by the additional drug cost stemming from improved persistence.

Sensitivity analyses show that the relationship between compliance and fracture risk greatly affects the changes in ICER in the case of changes in compliance. There is currently a debate regarding the nature of the association between compliance and relative risk of fracture. One study suggests a linear relationship for hip fracture [6], while others suggest that this association may be nonlinear, with essentially no fracture reduction at MPR values below 50% [7, 40]. The choice of analytic methods has also been shown to significantly impact the relationship between compliance and fracture risk [41]. Curtis et al. showed a linear relation between compliance and hip fracture risk reduction when considering MPR as a time-dependent variable (as in the study by Rabenda et al.) and a nonlinear relationship similar to that observed by Siris et al. when MPR was measured only at the end of the study [41]. Further research is therefore needed to explore the relationship between compliance and fracture risk.

The results of this study suggest that poor adherence related to oral bisphosphonates, far more than treatment efficacy, can be considered the critical hurdle in osteoporosis management. A recent study showed that improving

persistence by 20% could have the same clinical impact as a 20.2% increase in clinical efficacy [42]. Depending on cost, actions to improve adherence to therapy may be worthwhile in both clinical and economic terms. Poor adherence is, however, a complex phenomenon, and many determinants have been identified [43]. Strategies to overcome poor adherence have included health professional–patient relationship, treatment setting, and follow-up [44]. New formulations and dosage schemes, including oral monthly and quarterly or yearly intravenous treatment, have also been developed recently, which in principle could help to improve adherence to therapy [38]. In chronic diseases, less frequent dosing regimens have been associated with better adherence [45]. A weekly bisphosphonate was previously shown to improve adherence to therapy compared with daily bisphosphonate [6, 46]. Therapies with longer dosing intervals, such as yearly bisphosphonate injections, may therefore represent a promizing approach to reducing the clinical and economic burden of nonadherence to oral bisphosphonates. It is also interesting to note that a recent study suggested that persistence has significantly improved for patients who began bisphosphonate therapy [47]. These results may reflect the first effects of adherence-enhancing interventions, including the introduction of longer dosing regimens. Further research is, however, needed to assess adherence to these treatments in real-life settings and the potential cost-effectiveness of adherence-enhancing interventions.

This study also suggested that adherence has a marked impact on the cost-effectiveness of osteoporosis medications. Adherence is currently seldom included in cost-effectiveness analyses of osteoporosis medications [48]. The noninclusion of the effect of adherence in health economic modeling may lead to selection of suboptimal treatment strategies [2]. Therefore, compliance and persistence should be an integral part of pharmacoeconomic analyses in osteoporosis.

Measuring adherence and incorporating it into health economic modeling poses particular challenges. There are currently several gaps in empirical data preventing accurate incorporation of adherence data into pharmacoeconomic evaluations in osteoporosis [48]. More information is needed, for example, on the relationship between compliance and fracture risk and on the impact of treatment duration on the drug's efficacy, including offset time. Moreover, differences in methodology and patient demographics incorporated in the different studies available in the literature result in wide variations in adherence data. Country-specific data are required because many determinants affected by local conditions may influence adherence rates [43].

Assumptions were required in this study that may affect the results. First, an adjustment was made to account for suboptimal adherence in RCTs. Based on this adjustment, the fracture risk at an MPR value of 100% was reduced by 35% for hip fracture and by 81% clinical vertebral fracture for oral bisphosphonates. These values are very similar to those observed for once-yearly infusion of zoledronic acid, estimated at 41 and 77%, respectively [49]. Second, no further treatment was assumed for patients who discontinue therapy. A refill gap length of 5 weeks was used in the observational study to assess persistence [6], which is among the longest refill gaps periods used in prior studies [40]. However, some patients would return to therapy after this period [50]. Such patients may have an impact on the results, but they are difficult to include in modeling because the effectiveness of bisphosphonates used in an intermittent way is unknown. Other modeling assumptions included no treatment effect for patients in women who discontinued therapy at 3 months, an offset time of similar duration to therapy time, and a proportional relationship between drug cost and compliance. Although these assumptions may have a potential impact on the ICERs, they would not influence the general findings of this study. Another limitation of our study may be that we did not take into account the effect of age when estimating the impact of nonadherence. A recent study showed that the benefit of adherence with bisphosphonates depends on age [41]. A less marked impact of high adherence was also recently suggested for nonhip and nonvertebral fractures [41].

In conclusion, the results of this study suggest that nonadherence to osteoporosis medications results not only in worsening health outcomes, but also in a significant change in the cost-effectiveness of drug therapy. Adherence therefore remains an important challenge for healthcare professionals treating osteoporosis.

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