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The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients

Mickaël Hiligsmann[a,b,*], Véronique Rabenda[b], Olivier Bruyère[b], Jean-Yves Reginster[b]

[a] HEC-School of Management, University of Liège, Liège, Belgium
[b] Department of Public Health, Epidemiology and Health economics, University of Liège, Liège, Belgium

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ABSTRACT

Objectives: This study aims to estimate the clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients and the potential cost-effectiveness of adherence-enhancing interventions.
Methods: A validated Markov microsimulation model estimated costs and outcomes (i.e. the number of fractures and the quality-adjusted life-year (QALY)) for three adherence scenarios: no treatment, real-world adherence and full adherence over 3 years. The real-world adherence scenario employed data from a published observational study. The incremental cost per QALY gained was estimated and compared across the three adherence scenarios.
Results: The number of fractures prevented and the QALY gain obtained at real-world adherence levels represented only 38.2% and 40.7% of those expected with full adherence, respectively. The cost per QALY gained of real-world adherence compared with no treatment was estimated at €10 279, and full adherence was found to be cost-saving compared with real-world adherence.
Conclusions: This study suggests that more than half of the potential clinical benefits from oral bisphosphonates in patients with osteoporosis are lost due to poor adherence with treatment. Depending on their cost, interventions with improved adherence to therapy have the potential to be an attractive use of resources.

1. Introduction

Non-adherence with drug therapy is a major issue in health care, especially in chronic asymptomatic conditions such as postmenopausal osteoporosis. Since a wide variety of definitions for medication adherence have been used in the literature [1,2], it is important to define the terminology. Adherence is a general term encompassing two different constructs explained below, i.e. compliance and persistence. Medication compliance may be defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing of regimen" and medication persistence as "the length of time from initiation to discontinuation of therapy" [3]. Both compliance and persistence limit the drug potential benefit and may have significant clinical and economic implications [1,4]. In particular, non-adherence has been shown to be primarily driven by the issues of persistence [5].

Oral bisphosphonates are the most widely prescribed drugs for the treatment and prevention of postmenopausal osteoporosis [6]. Numerous clinical trials and meta-analyses have demonstrated that bisphosphonates significantly reduce the risk of vertebral and non-vertebral fractures [7–12]. However, their long-term efficacy is jeopardized in real-life settings by poor adherence. Many studies have reported suboptimal compliance and persistence among patients taking oral bisphosphonates [13,14]. For example, a large US study suggested that approximately

* Corresponding author at: HEC-School of Management, Department of Economics, University of Liège, Boulevard du Rectorat 7, Bât B31, 4000 Liège 1, Belgium. Tel.: +32 43663195; fax: +32 43662958.
E-mail address: m.hiligsmann@ulg.ac.be (M. Hiligsmann).

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three quarters of women who initiate bisphosphonate therapy are non-adherent within 1 year and 50% have discontinued therapy by this time [15]. Poor adherence leads to reduced effectiveness, lower gains in bone mineral density, and in turn results in higher fracture rates [16–18].

Although it is generally well accepted that adherence with osteoporosis medications is suboptimal in clinical practice, the clinical and economic impact of non-adherence has not been well described. Our goal was therefore to investigate the clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. More specifically, we first compared the clinical and economic outcomes obtained at real-world adherence levels with those expected with full adherence, in order to evaluate the potential loss of benefits resulting from poor adherence. Each component of medication adherence (i.e. compliance and persistence) was then individually evaluated to determine their influence on the results. Finally, we evaluated the potential cost-effectiveness (i.e. the cost per quality-adjusted life-year (QALY) gained) of adherence-enhancing interventions according to their cost and effect on adherence. Such information would be useful to inform policies that affect adherence with osteoporosis medications.

2. Materials and methods

A validated Markov microsimulation model [19] was used to compare costs and outcomes for three adherence scenarios: no treatment, real-world adherence and full adherence over 3 years after start of treatment. The real-world adherence scenario employed adherence data from a published Belgian observational study [18] and the full adherence scenario assumed that patients were fully adherent over 3 years.

The model employed a payer perspective, including direct healthcare costs paid by the national health insurance and the individual patient's out-of-pocket contribution, in accordance with methodological guidelines for pharmacoeconomic evaluations in the country of reference [20].

2.1. Microsimulation model

The Markov microsimulation model [19] was constructed and analysed using a decision analysis software (TreeAgePro 2006 Suite, release 0.4, TreeAge Software, Inc). The cycle length of the model was set to 1 year and a patient lifetime horizon was used. Each patient began in the no fracture state and had, every year, a certain probability of the following events: hip, clinical vertebral, wrist, or other fracture; no fracture; or death. The incidence of hip fracture was derived from a previous study [21], and the incidence of other fractures was imputed using fracture rates from other countries, assuming that the ratio between hip and other fractures would be similar between countries [21]. Each state had an associated cost and effectiveness, depending on patient characteristics. Transition costs included direct fracture costs in the year following the fracture and long-term costs beyond the first year for women institutionalized after a hip fracture. The direct cost of hip fracture was derived from previous studies [22,23] and the costs of clinical vertebral and other fracture were quantified relative to hip fracture on the basis of their costs [24,25]. Outcomes were expressed as number of hip and all osteoporotic fractures and in QALYs. The QALY estimator is an attractive outcome measurement in the field of osteoporosis because it offers the advantage of capturing the benefits from reductions in both morbidity and mortality [26]. Fracture disutility was modelled as a lower value for QALY and was derived from a systematic review of the literature [27]. Excess mortality was also assumed after hip and clinical vertebral fractures. Discount rates of 3.0% and 1.5% were assumed for cost (expressed in €2006) and effectiveness, respectively [20]. A detailed description and explanation of the model and data has been published elsewhere [19].

2.2. Target population

The target population was assumed to be uniformly distributed between 55 and 85 years of age and to have either a bone mineral density (BMD) *T*-score below −2.5 or a prevalent vertebral fracture, in order to match the two populations for whom postmenopausal osteoporosis medications are currently reimbursed in several European countries. In order to accurately reflect the risk in these populations, the risk of first fracture in the general population [21] was adjusted by relative risk parameters, using a previously validated method [28] and explained in detail elsewhere [29].

2.3. Drug therapy

Treated women were assumed to receive alendronate therapy, an oral bisphosphonate available with a weekly formulation. The clinical effectiveness of alendronate in the treatment of women with osteoporosis was derived from a recent meta-analysis conducted for the NICE appraisal and included large randomised controlled trials [11]. The relative risks *vs* placebo were therefore 0.62 (95% CI 0.40–0.96) for hip fracture, 0.55 (95% CI 0.40–0.66) for clinical vertebral fracture, 0.85 (95% CI 0.67–1.09) for wrist fracture and 0.83 (95% CI 0.74–0.93) for other fracture. The effect of treatment was assumed to linearly decline to zero after stopping therapy, during a duration (called offset-time) equal to the duration of therapy, in line with clinical studies [30,31] and assumptions used in previous models [32–34].

The cost of treatment included drug costs and costs of assessment. The annual cost of alendronate therapy was estimated at €308.3 (Fosamax®, €70.94 for a package of twelve 70 mg tablets, once per week [35]). In accordance with previous standard assumptions regarding the monitoring of osteoporotic treatments [26], treatment was associated with one yearly physician visit (€20.0) and one bone densitometry measurement every second year (estimated at €47.0). Adverse events were not included in the analysis since randomised studies of efficacy have not shown significant differences between placebo and actively treated patients [36].

2.4. Medication compliance and persistence

Medication adherence can be assessed using different methods [37]. Direct assessment methods (e.g. observation, serum drug concentration, biochemical analysis) are the most accurate methods for assessing adherence, but are costly and highly inconvenient [38]. Indirect methods of assessing adherence include patient interviews, self-report, pill counts and refill records [39]. Most studies assessing medication adherence have used pharmacy prescription refill records [40], which represents a reliable and inexpensive way of evaluating adherence [37].

In our analysis, the real-world adherence scenario employed adherence data from a recent published Belgian study, estimating both compliance to and persistence with alendronate therapy (daily and weekly combined) [18]. This study was a retrospective cohort analysis including pharmacy records of postmenopausal women who had received a first prescription for bisphosphonates between April 2001 and June 2004. Compliance to therapy was quantified as the number of doses taken divided by the number of doses prescribed, often called the "medication possession ratio (MPR)", and medication persistence was reported as the proportion of patients still taking medication at different time periods. A refill gap of 5 weeks was used to assess persistence [18], which is among the longest refill gaps periods used in prior studies [13].

Based on this study, 42.5% of women discontinued therapy within 6 months. For these women, no treatment effect was received and we assigned 3 months of therapy cost, as previously suggested [41]. Another 18.1% and 13.9% of women discontinued therapy at 1-year and 2-year, respectively. Therefore, only 25.5% of women received a 3-year treatment. It was assumed that if patients discontinue therapy, they received no further treatment and their offset-time was similar to the duration on therapy.

Women taking medication were considered to be compliant if their MPR was at least 80% in any given year and poorly compliant, otherwise. A MPR >80% was most commonly used to define high compliance [13]. The probabilities of being poorly compliant (i.e. MPR less than 80%) were estimated at 23.9%, 4.0% and 1.2% in the first, second and third year of treatment, respectively [18]. These women suffer from a lower treatment efficacy. Poor compliance was associated with a 35% increase in hip fracture rate (RR = 1.35, 95% CI 1.17, 1.56) in line with the Belgian study [18]. Because this study did not assess the relationship between compliance and non-hip fractures, we assumed a conservative 17% increase in other fractures rates (RR = 1.17, 95% CI 1.09–1.25) [42], for poorly compliant women. The relative risks from the systematic review were applicable to the population with compliance of 80% or greater. So, for instance, if alendronate was assumed to reduce the risk of hip fracture by 38%, then compliant women would experience a 38% reduction in hip fracture while poorly compliant women would experience only a 16.3% ($0.62 \times 1.35 = 0.837$) reduction in hip fracture. For poorly compliant women, drug cost was restricted to 80% of full price.

2.5. Analyses

First-order Monte-Carlo microsimulations were performed to estimate costs and outcomes (i.e. number of fractures and QALYs) for each adherence scenario. Each model was ran 10 times with 200 000 trials to enable variability analyses. The incremental cost-effectiveness ratio (ICER) was calculated between real-world adherence and no treatment scenarios, and between full adherence and real-world adherence scenarios. ICER was defined as the difference in terms of cost between strategies divided by their difference in terms of effectiveness (here measured as QALYs). An ICER represents the incremental cost per one QALY gained. Additional analyses estimated the cost-effectiveness of full adherence compared with real-world adherence at different starting age of treatment and for sub-populations of women aged 60, 70 or 80 years either with prevalent vertebral fracture or at the threshold for osteoporosis, i.e. a BMD *T*-score of −2.5 [36]. Mean ICER and 95% confidence interval were calculated for each simulation.

One-way sensitivity analyses were also performed to assess the impact of medication adherence assumptions on the results. These include modifications of persistence, compliance, MPR threshold for good compliance and drug cost for patients who discontinue therapy within 6 months. In particular, MPR thresholds of 70% and 90% for good compliance were examined. Poor compliance was associated with increases of 31% and 34% in hip fracture rates at these thresholds, respectively [18]. The probabilities of having a MPR lower than 90% were estimated at 28.8%, 25.4% and 23.0% in the first, second and third year of treatment. The same probabilities were 7.4%, 0.7% and 0.1% for a MPR of 70% [18].

Probabilistic sensitivity analyses were performed to assess the effects of uncertainty in all model parameters simultaneously. Log-normal distributions were assumed for fracture risk reduction with therapy and for increased risk related to poor compliance, as recommended by Briggs's book for relative risk parameters [43]. Distributions for other parameters have been published elsewhere [19,29]. Cost-effectiveness acceptability curves were constructed from the incremental cost and QALY for 150 second-order Monte-Carlo simulations. They show the probability of being cost-effective as a function of the threshold willingness to pay per QALY.

Additional simulations estimated the potential cost-effectiveness of adherence-enhancing interventions according to their cost (ranging from €0 to €300, per year) and effect on adherence (i.e. improvements of real-world adherence by 10%, 25% or 50%). We have not estimated the cost-effectiveness of a specific adherence-enhancing intervention but we aimed to explore the potential cost-effectiveness of such interventions, suggesting that interventions with improved adherence to therapy exist or could be developed. They included adherence programs (such as educational program) and new products with better adherence profile. A recent review suggested that few interventions to improve adherence and persistence with osteoporosis medications were efficacious and that those reporting a statistically significant improvement

Table 1
Base-case analysis.

	Adherence scenario			Incremental values	
	No treat	Real-world	Full	RW *vs* NoTr	Full *vs* RW
Patient cost over lifetime (€2006)					
Treatment cost	0	468.88	970.18	468.88	501.30
Disease cost	10 194.79	9862.55	9353.10	−332.23	−509.46
Total cost	10 194.79	10 331.43	10 323.28	136.65	−8.16
Lifetime number of fractures per patient					
Hip	0.3961	0.3866	0.3714	−0.0095	−0.0152
Overall	1.1203	1.0974	1.0604	−0.0229	−0.0370
QALYs per patient	10.6036	10.6170	10.6366	0.0134	0.0196
ICER (cost per QALY gained)				10 279	−428
(95% CI)				(7536, 14 197)	(−1732, 689)

CI: confidence interval, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life-year, RW: real-world.

in adherence were associated with effect sizes from 0.17 to 0.58 [44], supporting the proposed improvements in adherence.

3. Results

3.1. Base-case analysis

The results of the base-case analysis are presented in Table 1. Average values were estimated for the three adherence scenarios and incremental values were calculated for the real-world adherence scenario compared with no treatment and for the full adherence scenario *vs* real-world adherence.

Mean lifetime cost per patient (in €) was 10 195 (95% CI 10 122, 10 283) for the no treatment scenario, 10 331 (95% CI 10 261, 10 384; $P < 0.0001$) for the real-world adherence scenario and 10 323 (95% CI 10 252, 10 375; $P = 0.077$ between adherence scenarios) for the full adherence scenario. Total cost was therefore lower in the full adherence scenario than in the real-world adherence scenario, as the averted costs of treating additional osteoporotic fractures resulting from the non-adherence (i.e. 509.46) exceed the cost of the additional therapy stemming from the improved adherence (i.e. 501.30).

Effectiveness was measured as the number of hip and all osteoporotic fractures, and as quality-adjusted life-years. Mean number of hip fracture per patient was 0.3961 (95% CI 0.3938, 0.3993) for the no treatment scenario, 0.3866 (95% CI 0.3843, 0.3896) for the real-world scenario and 0.3714 (95% CI 0.3693, 0.3743) for the full adherence scenario. The equivalent values for all osteoporotic fractures were 1.1203 (95% CI 1.1143, 1.1268), 1.0974 (95% CI 1.0910, 1.1037) and 1.0604 (95% CI 1.0544, 1.0667), respectively. Therefore, the number of hip and all osteoporotic fractures prevented in the case of real-world adherence represent 38.4% (95% CI 36.8%, 41.0%) and 38.2% (95% CI 37.7%, 39.0%) to that estimated with full adherence scenario, respectively. Mean lifetime QALYs, discounted by 1.5%, were estimated at 10.6036 for the no treatment scenario, 10.6170 for the real-world scenario and 10.6366 for the full adherence scenario. The QALYs gained in the real-world adherence scenario therefore represents 40.8% (95% CI 36.2%, 45.8%) to that obtained under full adherence scenario.

Compared with no treatment, real-world adherence scenario was associated with an additional cost of €136.65 and a QALY gain of 0.0134, giving an ICER of €10 279 per QALY gained (95% CI 7536, 14 197). The full adherence scenario was associated with a lower cost and a higher QALY than the real-world adherence scenario, giving a negative

Table 2
One-way sensitivity analyses on the clinical and economic burden of non-adherence with oral bisphosphonates.

	Clinical burden	Economic burden (ICER)[a]	
	% of QALY gain[b]	Scenario *vs* NoTr	Full *vs* scenario
Base-case analysis	40.8%	10 279	−428
Starting age of treatment: 60 years	40.4%	30 449	17 701
Starting age of treatment: 70 years	39.5%	10 409	1577
Starting age of treatment: 80 years	40.4%	−7356	−23 557
Full compliance	42.9%	7898	242
Full persistence	96.9%	5334	−17 604
MPR of 90% for good compliance	36.9%	12 070	−967
MPR of 70% for good compliance	41.6%	7732	−75
Cost of 4 weeks alendronate for patients who discontinue therapy within 6 months	40.8%	8807	587

BMD: bone mineral density, CI: confidence interval, MPR: medical possession ratio, NOTR: no treatment, QALY: quality-adjusted life-year.

[a] Incremental cost-effectiveness ratio (expressed in € per QALY gained) of the simulated scenario compared with no treatment and full adherence scenario.

[b] Percentage of QALY gain for the simulated scenario compared to that obtained with the full adherence scenario.

ICER of €-428 per QALY (95% CI −1732, 689). Full adherence is said to be cost-saving compared with real-world adherence.

3.2. One-way and probabilistic sensitivity analyses

The cost (in €) per QALY gained of the full adherence scenario compared with real-world adherence scenario was highly sensitive to baseline population risk. For women at the threshold of osteoporosis (i.e. BMD *T*-score of −2.5) and no prior fracture, the ICER was estimated at 24 001 (95% CI 19 375, 26 909), 11 975 (95% CI 9115, 15 320) and at −2 830 (95% CI −4551, −1840) at the ages of 60, 70 and 80 years, respectively. The equivalent values were 19 744 (95% CI 16 790, 23 905), 3965 (95% CI 2477, 5187) and −17 691 (95% CI −20 985, −16 080) for women with prevalent vertebral fracture, respectively.

As observed in Table 2, the clinical burden of non-adherence with oral bisphosphonates was not affected by the age at start of treatment, while the ICER greatly improved with increasing age of treatment. Additional sensitivity analyses showed that adherence is primarily driven by persistence. When assuming full persistence, the clinical burden of compliance is very limited. Other analyses showed moderate clinical and economic impact of MPR thresholds for good compliance and of drug cost for patients who discontinue therapy within 6 months.

Cost-effectiveness acceptability curves show the probability of being cost-effective as a function of the decision maker's willingness to pay (Fig. 1). The real-world adherence scenario was cost-effective compared with no treatment in 69.3% 83.3% and 92.3% of the cases for threshold values of €20 000, €30 000 and €40 000 per QALY gained, respectively. The full adherence scenario was shown to be cost-saving (i.e. ICER being below €0 per QALY) compared with the real-world adherence scenario in 48.0% of the cases, i.e. the ICER fell below the threshold value 72 times out of the 150 simulations. The probability of full adherence being cost-effective increased to 97.3% considering a willingness to pay of €30 000 per QALY gained.

3.3. Adherence-enhancing interventions

Fig. 2 presents the cost-effectiveness of adherence-enhancing interventions according to their cost and effect on adherence. The cost (in €) per QALY gained of such interventions is graphically presented by the black lines and the grey lines represent the lower and upper limits of the 95% confidence interval.

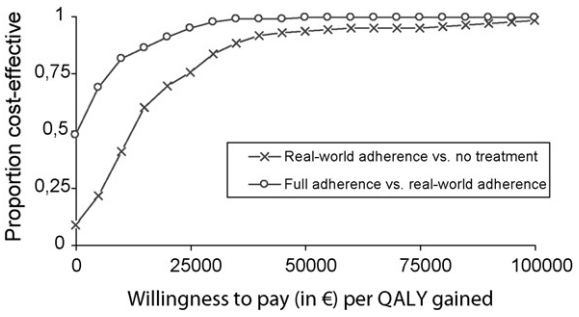

Fig. 1. Cost-effectiveness acceptability curves. The curves show the probability of being cost-effective as a function of the decision maker's willingness to pay per one QALY. QALY: quality-adjusted life-year.

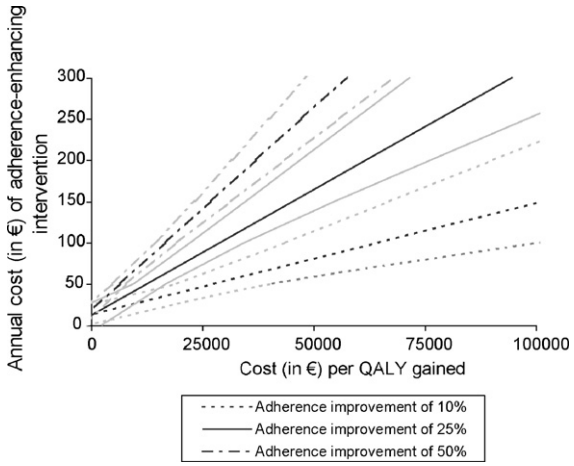

Fig. 2. The cost-effectiveness (expressed in cost (in €) per QALY gained) of adherence-enhancing interventions according to their cost and effect on adherence. The cost-effectiveness is graphically presented by the black lines and the grey lines represent the lower and upper limits of the 95% confidence interval. QALY: quality-adjusted life-year.

For example, interventions that would improve adherence by 25% would be associated with an ICER of €/QALY 12 653 (95% CI 9689, 16 909) and €/QALY 29 073 (95% CI 22 374, 34 586) if they cost €50 and €100 per year, respectively. For potential interventions associated with a 50% increase in adherence rates, their cost-effectiveness were estimated at €/QALY 16 768 (95% CI 14 417, 19 359) and €/QALY 37 142 (95% CI 31 797, 43 657) for additional annual costs of €100 and €200, respectively.

When assuming that interventions only affect persistence, moderate increase in the ICER was observed. So, interventions that would improve persistence by 25% would be associated with an ICER of €/QALY 15 102 and/QALY 32 210 if they cost €50 and €100 per year, respectively. For strategies associated with a 50% increase in persistence rates, their ICER were estimated at €/QALY 18 832 and €/QALY 40 337 for annual costs of €100 and €200, respectively.

4. Discussion

Poor adherence with osteoporosis medications reduces the drug potential benefit and has significant clinical and economic implications. We estimated in this study the clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients, by comparing the clinical outcomes and the cost-effectiveness of real-world adherence with full adherence.

The results of this study suggest that the number of fractures prevented and the QALY gain obtained with real-world adherence levels represented only 40% of those expected with full adherence. Moreover, although oral bisphosphonates have been shown to be cost-effective at adherence levels seen in real-life settings, they become

more cost-effective with improved adherence and the full adherence scenario was shown to be cost-saving (i.e. less costly and more effective) compared with the real-world adherence scenario. Strategies to improve adherence are therefore needed to reduce the considerable burden of non-adherence with oral bisphosphonates. Because such interventions are rarely cost-free, we estimated how cost-effective they should be to be considered worthwhile.

Non-adherence was shown to be primarily driven by the issues of persistence, as observed in hypertension [5]. This finding cannot be interpreted as the lack of impact of compliance on the clinical and economic outcomes of osteoporosis medications, but may be explained by high compliance in patients taking therapy. So, the probabilities of being good compliant (i.e. MPR > 80%) were estimated, in the observational study, at 96.0% and 98.8% in the second and the third year of treatment. If more patients would have been bad compliant, which may be the case in other countries, the impact of compliance on the burden of non-adherence would have been probably much more higher.

Studies in other countries have also shown that compliance and persistence with osteoporosis medications have clinical and/or economic implications. Some studies have specifically investigated the effects of changing the dosing regimens of bisphosphonates and improvements of persistence and compliance on the number of fractures prevented [45–48]. The cost-effectiveness of these new dosing regimens was also shown to be better than weekly and daily oral bisphosphonate [46]. Indeed, non-adherence with osteoporosis medications may substantially increase the ICER of osteoporosis strategies [11,49], and especially in the presence of the upfront cost of case-finding (such as screening cost) [50]. The present study adds to the literature by estimating, in the same analysis, the impact of both compliance and persistence on clinical (i.e. the number of fractures prevented and the QALY gain) and economic outcomes, in order to evaluate the potential loss of benefits resulting from poor adherence.

Our analysis may also provide an interesting framework for evaluating the cost-effectiveness of adherence-enhancing interventions. We have not examined the feasibility and acceptability of a specific adherence-enhancing intervention but we aimed to explore the potential cost-effectiveness of such interventions, according to their cost and effect on adherence. Improving adherence with osteoporosis medications is however a complex and challenging issue. Many determinants of poor adherence have been identified and include side effects, inconvenient dosing regimens, lack of motivation and medication cost [51–53]. Beliefs about treatments may also differ between physicians and patients, making it difficult to achieve consensus about the best treatment. In recent years, many programs have been initiated to improve adherence but few strategies have demonstrated clear improvements in clinical outcomes and multifaceted interventions should be highly encouraged [44]. Strategies to improve adherence have included follow-up interaction between health professionals and patients, educational intervention and longer dosing intervals. In particular, some studies have suggested that implementing monitoring or giving feedback to patients, such as BMD information or bone turnover marker, as a tool to improve medication adherence, may result in a improved outcome [54,55]. Understanding patient's preferences for osteoporosis treatments and involving patients into clinical decision-making may also contribute to optimise treatment selection and to improve adherence to therapy. New formulations and dosages schemes, such as yearly bisphosphonate injections, have been recently developed, which in principle can help to improve adherence [16]. Less frequent dosing regimens have been frequently associated with better adherence [56]. Our results suggest that therapies that optimise adherence would remain cost-effective compared with oral bisphosphonates even if they cost up to €100 or €150 more, per year. Further studies are however needed to assess adherence with such regimens in real-life settings and their cost-effectiveness compared with oral bisphosphonates.

The methodology to incorporate adherence into health economic modelling was conceptionally close to that suggested by Ström et al. [41], with a large difference. In contrast to this study, we integrated real-world estimates for compliance. Patients taking medication were classified as compliant (MPR ≥ 80%) or partially compliant (MPR < 80%). The proportions of these groups were derived for any given year [18] and partially compliant patients were assumed to be associated with an increased risk of fractures [18,42]. Drug cost was also adjusted for poorly compliant patients. This modelling methodology represents an important innovation to incorporate compliance into health economic modelling of osteoporosis.

Our analysis should be interpreted in light of these limitations, including assumptions and data on adherence. First, no further treatment was assumed for patients who discontinued therapy. To assess persistence, a refill gap period of 5 weeks was used in the observational study [18], which is among the longest refill gap periods used in previous studies [13]. However, we cannot exclude that some patients would return to therapy after this period. A recent study identified particular patients who return from temporary interruptions in therapy [57]. Such patients may affect the burden of non-adherence but are difficult to include in modelling because the effectiveness of oral bisphosphonates used in an interrupted way is unknown. Second, patients were assumed to be poorly compliant if their MPR was below 80%. This group will however be diverse in their levels of compliance, which would influence the effect of therapy on fracture risk and the cost of therapy. However, a vast majority of poorly compliant patients had a MPR between 50% and 80% in the observational study [18] and they were therefore not divided into smaller intervals. The use of a threshold of 80% for good compliance might also be questionable since there is no clinically meaningful definition for good compliance. However, a MPR of 80% was most commonly used to define high compliance [13]. Sensitivity analyses with other MPR thresholds suggested a limited impact on the results. Third, drug cost was assumed to be 100% and 80% of full price for compliant and poorly compliant women, respectively. However, it is likely that some patients in both groups would not support these costs. Given that mean MPR was not available, we conservatively assumed high drug cost for both groups. Fourthly, assigning 3 months for women

who discontinue within 6 months might not be realistic, depending on prescribing customs. Alendronate is currently available, in the reference country, with prescription for 4 or 12 weeks. A sensitivity analyses was therefore performed with the cost of a 4-week tablet. Finally, a modelling approach was necessary to simulate the clinical outcomes and costs of the different scenarios over longer periods of time. All modelling requires simplifying assumptions which may sometimes be difficult to validate. The simulation model used here has however been previously validated [19].

Our study emphasizes that adherence remains an important challenge for healthcare professionals treating osteoporosis, but the concept extends beyond this disease area. Previous studies have shown that non-adherence have significant clinical and/or economic impact in hypertensive patients [58], in renal transplantation [59] or in diabetes [60]. Health economic modellers should therefore continue to be aware of this potential impact [59].

5. Conclusions

The results of this study suggest that more than half of the potential clinical benefits of oral bisphosphonates in patients with osteoporosis are lost due to poor compliance and failure to persist. Moreover, non-adherence substantially affects the cost-effectiveness of osteoporosis drugs, and should therefore be included in pharmacoeconomic analyses. Strategies to improve adherence are therefore needed and, depending on their cost, have the potential to be an attractive use of resources.

Conflict of interest

Mickaël Hiligsmann, Olivier Bruyère and Jean-Yves Reginster have received research grants and/or consulting fees from pharmaceutical companies.

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