The Clinical and Economic Burden of Poor Adherence and Persistence with Osteoporosis Medications in Ireland

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Abstract

Objectives: Medication nonadherence is common for osteoporosis, but its consequences have not been well described. This study aimed to quantify the clinical and economic impacts of poor adherence and to evaluate the potential cost-effectiveness of improving patient adherence by using hypothetical behavioral interventions. Methods: A previously validated Markov microsimulation model was adapted to the Irish setting to estimate lifetime costs and outcomes (fractures and quality-adjusted life-year [QALY]) for three adherence scenarios: no treatment, real-world adherence, and full adherence over 3 years. The real-world scenario employed adherence and persistence data from the Irish Health Services Executive-Primary Care Reimbursement Services pharmacy claims database. We also investigated the cost-effectiveness of hypothetical behavioral interventions to improve medication adherence (according to their cost and effect on adherence). Results: The number of fractures prevented and the QALY gain obtained at real-world adherence levels represented only 57% and 56% of those expected with full adherence, respectively. The costs per QALY gained of real-world adherence and of full adherence compared with no treatment were estimated at €11,834 and €6,341, respectively. An intervention to improve adherence by 25% would result in an incremental cost-effectiveness ratio of €11,511 per QALY and €54,182 per QALY, compared with real-world adherence, if the intervention cost an additional €50 and €100 per year, respectively. Discussion: Poor adherence with osteoporosis medications results in around a 50% reduction in the potential benefits observed in clinical trials and a doubling of the cost per QALY gained from these medications. Depending on their costs and outcomes, programs to improve adherence have the potential to be an efficient use of resources. Keywords: adherence, cost-effectiveness, intervention, osteoporosis, persistence.

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Introduction

The management of osteoporosis is becoming a major priority in public health. At least one in three women older than 50 years, and one in five men, will suffer an osteoporotic fracture in their remaining lifetime [1]. These fractures result in significant morbidity and mortality and reduction in quality of life and pose considerable costs to already stretched health care systems [2,3]. Figures derived from the International Osteoporosis Foundation estimate that approximately 300,000 people older than 50 years have osteoporosis in Ireland. This figure represents 25% of this population. The results of an Irish Burden of Illness Study demonstrated that fall-related injuries in the elderly cost the Irish health care system approximately €402 million each year [4]. With an increasingly elderly population and longer life expectancy, the burden is set to increase.

Fortunately, an increasing number of pharmacological agents have become available in the last 10 years for the treatment of low bone mineral density (BMD). Numerous clinical trials and meta-analyses have shown that antosteoporosis medications and in particular the oral bisphosphonates significantly reduce the risk of both vertebral and nonvertebral fractures [5]. In addition, economic analyses, typically based on efficacy estimates drawn from clinical trials, have consistency shown these medications to be cost-effective in a wide range of patient profiles for both primary and secondary prevention [6,7].

Despite the availability of proven effective pharmacotherapy for managing osteoporosis, studies are continuing to show that postfracture treatment with antosteoporotic medications remains suboptimal [8,9]. Furthermore, in more recent years, the issue of nonadherence with drug therapy, particularly in chronic asymptomatic diseases such as osteoporosis, further compromises the clinical and economic effects of the management of these patients. Adherence to treatments in patients with osteoporosis has been found to be suboptimal in several studies [10–12]. These studies have concluded that between 50% and 75% of patients who were initiated on antosteoporotic medications have discontinued their medications within 12 months of commencement. Although it is well recognized that poor adherence reduces
the potential benefits of osteoporosis therapy, lowering gains in BMD resulting in increased risk of fragility fractures [13], the clinical and economic consequences at a population level have been rarely studied [14,15]. A few studies carried out to date have however suggested potential important clinical and/or economic implications of poor adherence to osteoporosis medications [16–19].

Adherence is influenced by health beliefs such as risk perception, perceived benefits and disadvantages of drugs, self-efficacy, and stage of change and communication problems with physicians [20]. Over recent years, behavioral interventions to improve patient adherence have been developed [21,22]. Although their effectiveness still requires further validation, educational programs and patient counseling by nurses may be effective in improving patient adherence. New therapeutic options with longer dosing regimens have also been recently available for the prevention and treatment of osteoporosis that may, at least in principle, further help to increase adherence. Under limited resources, it is becoming increasingly important to examine how cost-effective an intervention should be in order for it to be considered worthwhile. Using simulation modeling, which allowed us to capture the long-term effects of medications, this study aimed to quantify the clinical and economic effects of poor adherence with osteoporosis medications in Ireland and to estimate the potential cost-effectiveness of hypothetical interventions to improve medication adherence according to their cost and effect on adherence.

Methods

A published and validated Markov microsimulation model on the natural history of osteoporosis was developed by Hiligsmann et al. [23] and has been frequently used to assess the cost-effectiveness of osteoporosis management in Belgium [18,24–28]. The model was recently updated with a 6-month cycle length to estimate the cost-effectiveness of denosumab [28]. We used this updated model to assess the clinical and economic burden of poor adherence from the Irish public health care perspective, that is, the Health Services Executive (HSE). The model was programmed by using the software TreeAge Pro 2011 (TreeAge Pro, Inc., Williamston, MA).

The simulation model estimated fracture events, costs, and quality-adjusted life-years (QALYs) for three adherence scenarios: no treatment, real-world adherence, and full adherence. The "no-treatment" scenario included no costs and no benefits of treatment. The real-world scenario employed adherence and persistence data from the Irish HSE-Primary Care Reimbursement Services (HSE-PCRS) pharmacy claims database for all treatment-naive patients older than 55 years who started osteoporosis medications in Ireland between 2006 and 2009, and the full-adherence scenario assumed that patients were fully adherent over 3 years. Patients therefore received treatment in the model for a maximum of 3 years, because most clinical trials last only 3 years and adherence data were collected over this period. The model simulated a patient’s lifetime (i.e., until death or 100 years), however, to capture all relevant costs and consequences of fractures experienced during the treatment period.

A description of the different components of the model is outlined in this section. Most model data are included in Table 1. More details can be found in Appendix 1 in Supplemental Materials found at doi: 10.1016/j.jval.2012.02.001. Please also refer to previously published research [17,23] for limitations of the model and an illustration on how the model integrates memory [23].

Model structure

Figure 1 provides an overview of the model. The model health states are no fracture, death, hip fracture, clinical vertebral fracture, wrist fracture, other fracture, and the corresponding post-fracture states. Postfracture states were created because some parameters (e.g., fracture disutility) were estimated over a 1-year period [28]. All the patients, one at a time, began in the “no-fracture” state and every 6 months had a probability of having a fracture of the hip, clinical vertebrae, wrist, or other site or dying. Patients in a fracture state can stay in the same fracture state if they refracture, change to another fracture state, die, or change in the next cycle to the postfracture state. Patients being in any postfracture state might have a new fracture (all fracture types are possible), die, or move to the "no-fracture" state. Tracker variables were created to record the number of each fracture type and used to adjust transition probabilities, costs, and utilities to reflect the impact of prior fractures.

Fracture incidence and mortality rates

Analyses were assessed in patients receiving osteoporosis medications. In Ireland at present, there are no conditions attached for the reimbursement of antosteoporosis therapies. Unlike the United Kingdom and other European countries, Ireland has access to unlimited prescribing of these products. Therefore, clinicians make their decision on whether or not to prescribe these products on the basis of the results of densitometry and BMD levels, history of fracture, risk factors, and so on. In this study, we assumed that all treated patients have the same risk as patients with osteoporosis, based on the definition of the World Health Organization (i.e., BMD T score of ≤−2.5). All patients were therefore assumed to have the same base-case risk before treatment efficacy is impacted.

To accurately reflect the risk of patients with a BMD T score of ≤−2.5 in comparison with that of the general population, the risk of fracture in the general population was adjusted by relative risk (RR) parameters, using a previously validated method [30] (see Appendix 1 for further details in Supplemental Materials found at doi: 10.1016/j.jval.2012.02.001). The incidence of hip fractures in the general population was derived from the Health Atlas Ireland, for the year 2008 (http://www.hse.ie/eng/services/maps/). Because the incidence of other fractures was not known, we assumed that the age- and sex-specific ratio of index fracture to hip fracture in Ireland was the same as found in Sweden [1]. This assumption, used in the development of many FRAX models [36], appears to hold true for West European countries, the United States, and Australia [37].

Age-specific mortality rates are available from the Central Statistics office in Ireland, and excess mortality was modeled after hip and vertebral fractures [31]. Because excess mortality may be attributable to comorbidities, we conservatively assumed that only 25% of the excess mortality following a hip or vertebral fracture could be directly or indirectly attributable to the fractures themselves [38,39].

Fracture cost

The perspective of the public health care payer (i.e., the HSE) was adopted for all cost estimates. Only direct medical costs were reported. All costs were reported as 2008 values. Direct hip fracture costs are divided into hospitalization cost (in the first cycle following the fracture) and long-term costs for patients being institutionalized following the fracture. The hospitalization cost of hip fracture was obtained from the Hospital In-Patient Enquiry system for 2008 and the associated Disease Related Group costs (http://www.healthatlasireland.ie). The cost of nursing home was selected from the average cost of approved private nursing homes in Dublin North East and Dublin Mid Leinster (N = 185) (requested from the HSE), and the probability of admissions to a nursing home after a hip fracture was derived from the study of Beringer et al. [32]. Of 2034 subjects (men and women) living at home at the time of fracture, 10% were in

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Clinical vertebral; FX, fracture. "Death" and "No Fx" were excluded from the graph for simplicity. CV, clinical vertebral; FX, fracture.

Other fractures included humerus, tibia/fibula, pelvis, and ribs fractures.

Incidence (annual rate/1000 persons-years)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women</th>
<th>Men</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture</td>
<td>1.12 (60–64 y), 1.99 (65–69 y), 4.73 (70–74 y), 9.80 (75–79 y), 17.47 (80–84 y), 32.97 (85 + y)</td>
<td>0.62 (60–64 y), 1.51 (65–69 y), 2.02 (70–74 y), 5.68 (75–79 y), 10.69 (80–84 y), 20.01 (85 + y)</td>
<td>[29]</td>
</tr>
<tr>
<td>CV fracture</td>
<td>1.75 (60–64 y), 2.81 (65–69 y), 6.67 (70–74 y), 8.32 (75–79 y), 9.42 (80–84 y), 14.63 (85 + y)</td>
<td>1.97 (60–64 y), 1.81 (65–69 y), 3.38 (70–74 y), 5.61 (75–79 y), 6.56 (80–84 y), 14.13 (85 + y)</td>
<td>[1]</td>
</tr>
<tr>
<td>Wrist fracture</td>
<td>3.28 (60–64 y), 4.42 (65–69 y), 7.75 (70–74 y), 7.73 (75–79 y), 9.78 (80–84 y), 12.36 (85 + y)</td>
<td>1.22 (60–64 y), 2.11 (65–69 y), 0.60 (70–74 y), 1.59 (75–79 y), 1.82 (80–84 y), 3.82 (85 + y)</td>
<td>[1]</td>
</tr>
<tr>
<td>Other fracture*</td>
<td>2.55 (60–64 y), 4.98 (65–69 y), 6.77 (70–74 y), 13.07 (75–79 y), 15.40 (80–84 y), 35.10 (85 + y)</td>
<td>2.31 (60–64 y), 5.56 (65–69 y), 5.18 (70–74 y), 6.91 (75–79 y), 22.47 (80–84 y), 28.67 (85 + y)</td>
<td>[1]</td>
</tr>
</tbody>
</table>

Relative risk of fracture attributable to osteoporosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women</th>
<th>Men</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture</td>
<td>3.39 (60–64 y), 2.25 (70–74 y), 1.57 (80 + y)</td>
<td>4.76 (60–64 y), 3.58 (70–74 y), 2.05 (80 + y)</td>
<td>[30]</td>
</tr>
<tr>
<td>CV fracture</td>
<td>2.18 (60–69 y), 1.77 (70–74 y), 1.51 (80 + y)</td>
<td>2.65 (60–64 y), 2.39 (70–74 y), 1.93 (80 + y)</td>
<td>[30]</td>
</tr>
<tr>
<td>Wrist fracture</td>
<td>1.61 (60–69 y), 1.43 (70–74 y), 1.30 (80 + y)</td>
<td>1.81 (60–69 y), 1.70 (70–74 y), 1.50 (80 + y)</td>
<td>[30]</td>
</tr>
<tr>
<td>Other fracture</td>
<td>1.90 (60–69 y), 1.61 (70–74 y), 1.42 (80 + y)</td>
<td>2.23 (60–64 y), 2.05 (70–74 y), 1.73 (80 + y)</td>
<td>[30]</td>
</tr>
</tbody>
</table>

Excess mortality after hip and clinical vertebral fracture

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women</th>
<th>Men</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 mo, 6–12 mo, subs year</td>
<td>4.53, 1.75, 1.78</td>
<td>5.75, 2.31, 1.69</td>
<td>[31]</td>
</tr>
</tbody>
</table>

Direct fracture costs (in €2008)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women</th>
<th>Men</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip, first 6 mo</td>
<td>From 11,215 to 13,140</td>
<td>From 12,053 to 14,042</td>
<td>[29]</td>
</tr>
<tr>
<td>Hip, yearly long-term costs</td>
<td>From 4,449 to 4,805</td>
<td>From 4,523 to 4,845</td>
<td>[31,32]</td>
</tr>
<tr>
<td>CV, first 6 mo</td>
<td>From 1,950 to 2,285</td>
<td>From 2,096 to 2,442</td>
<td>[33]</td>
</tr>
<tr>
<td>Wrist, first 6 mo</td>
<td>From 1,624 to 1,903</td>
<td>From 1,746 to 2,034</td>
<td>[33]</td>
</tr>
<tr>
<td>Other, first 6 mo</td>
<td>From 1,947 to 2,281</td>
<td>From 2,093 to 2,438</td>
<td>[33]</td>
</tr>
</tbody>
</table>

Health states utility values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women</th>
<th>Men</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>0.83 (60–69 y), 0.77 (70–79 y), 0.72 (80 + y)</td>
<td>0.84 (60–69 y), 0.78 (70–79 y), 0.71 (80 + y)</td>
<td>[34]</td>
</tr>
<tr>
<td>Hip (first year/subs year)*</td>
<td>0.80/0.90</td>
<td>0.80/0.90</td>
<td>[34]</td>
</tr>
<tr>
<td>CV (first year/subs year)*</td>
<td>0.72/0.93</td>
<td>0.72/0.93</td>
<td>[34,35]</td>
</tr>
<tr>
<td>Wrist (first year/subs year)*</td>
<td>0.94/1.00</td>
<td>0.94/1.00</td>
<td>[34,35]</td>
</tr>
<tr>
<td>Other (first year/subs year)*</td>
<td>0.91/1.00</td>
<td>0.91/1.00</td>
<td>[34]</td>
</tr>
</tbody>
</table>

CV, clinical vertebral; subs, subsequent.

* Other fractures included humerus, tibia/fbula, pelvis, and ribs fractures.

† Relative reduction in health utility value (represents the proportional loss of QALY due to the fracture).

Fig. 1 – Model structure. Transitions to death and from postfracture states to any fracture states. “Death” and “No Fx” were excluded from the graph for simplicity. CV, clinical vertebral; FX, fracture.

Nursing home care after 1 year. Because patients might be institutionalized later in life in any case, regardless of their hip fracture, an adjustment was made to only include long-term costs attributable to the fracture itself [23].

Nonhip fractures have been quantified relative to hip fracture on the basis of their costs [33]. So, the costs of clinical vertebral, wrist and other fracture represent 17.4%, 14.5%, and 17.4% of the acute hip fracture cost, respectively. Nonhip fractures were conservatively assumed to be not associated with long-term costs.

Fracture disutility

Utility values for the general population as well as relative reductions due to fractures in the year following the fracture and in subsequent years were derived from a recent systematic review, which suggested reference values for countries that do not have their own database [34]. The model took into account that the number of fractures is a predictor of quality of life. In the case of an occurrence of a second fracture at the same site, the impact of the first fracture event was reduced by 50%, as previously suggested [23]. For example, if a patient with a prior hip fracture suffered another hip fracture, the relative reduction of utility attributable to the first hip fracture was then 0.95 and the total reduction of utility attributed to both fractures was therefore 0.76 (≈0.95 × 0.80) in the year following the fracture. For an individual with both a hip fracture and a vertebral clinical fracture, the total impact on QALY was assumed to be equal to the sum of the impacts related to each of the fractures [26].

Drug therapy

Treated patients were assumed to receive the effectiveness of oral bisphosphonates, the most widely prescribed antosteoporosis...
medications in Ireland and worldwide. The clinical effectiveness of oral bisphosphonates in the treatment of women with osteoporosis was derived from a recent meta-analysis conducted for the National Institute for Health and Clinical Excellence appraisal and included large randomized controlled trials on alendronate and risedronate [40]. The RRs of fracture in the treatment group versus the placebo group were 0.71 for hip fracture, 0.58 for clinical vertebral fracture, and 0.78 for wrist and other fractures assuming the RR for other nonvertebral 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 [41]. The mean annual drug cost for patients taking osteoporosis medications in Ireland was estimated at €422.3 for women and at €417.0 for men. The costs of the drugs are taken from the HSE-PCRS. In this particular scheme, there is no co-payment for the patients. Monitoring cost includes one yearly physician visit (€65, HSE, http://www.hse.ie) and one bone densitometry measurement every second year (estimated at €90, Irish Osteoporosis Society, http://www.irishhealth.com/article.html?id=7099). Adverse events were not included in the analysis because randomized studies have not shown significant differences between placebo and actively treated patients [5].

**Medication adherence**

Adherence data were obtained from the Irish HSE-PCRS database, formerly the General Medical Services Payments Board scheme. This scheme provides free health care to approximately 30% of the Irish population (approximately 1.2 million). Eligibility for the scheme is means tested for those younger than 70 years and is confined to persons who are unable without undue hardship to arrange general practitioner services for themselves and their dependents. Patients registered under this scheme are dispensed all medicines free of charge. From July 2001 to December 2008, the service has been made available to all those older than 70 years. While the HSE-PCRS population cannot be considered representative of the entire population, because the elderly and the socially disadvantaged are overrepresented, it is estimated to account for approximately 70% of all medicines dispensed in primary care. National prescription file were analyzed for the years 2006–2009 to identify all prescription items relating to medicines dispensed for the management of osteoporosis (Anatomical Therapeutic Chemical classification system code M05B) in all patients aged 55 years and older. New users of antosteoporosis medications were defined as those not receiving any medication for osteoporosis in the previous 12 months. The final adherence database included a total of 70,669 women and 12,613 men, with the majority of these aged older than 75 years.

Both persistence and adherence to treatment were measured by using the pharmacy claims database. Persistence is defined as “the duration of time from initiation to discontinuation of treatment” [42]. Persistence was defined as a dichotomized variable (persistent or not) as to whether a patient continued therapy beyond an elapsed time period. In this study, we vary the time periods (i.e., 6 months to 3 years) and a permissible gap of 90 days was selected in the base-case as monthly regimens were included in the database. In the subgroup of persistent patients, adherence was calculated as the medication possession ratio (MPR), which is the ratio between the numbers of days of medication supplied to the number of days in a time interval. Adherence can be dichotomized (adherent or nonadherent) according to the MPR. The conventional approach is to use a cutoff of 0.8 [43], but this was varied in sensitivity analysis. Patients with a MPR greater than or equal to 0.8 were therefore considered to be adherent, in the base-case analysis. The probability of patients restarting therapy 1 year after stopping was also estimated. All analyses were performed by using SAS (version 9.1, SAS Institute Inc., Cary, NC).

In the model, patients were at risk of discontinuation within 3 years. For patients who stopped taking their therapy, the treatment cost was stopped in the middle of the dropout cycle and the offset-time period started at the same time. For those who discontinued therapy within 6 months, no treatment effect was received [44], because at least 6 months of treatment is necessary to reduce the risk of fractures [45,46]. The mean drug cost of these patients, administrated in the first cycle of the model, was specifically estimated at €119.13 for women and at €97.40 for men (HSE-PCRS database). Patients who discontinued therapy can restart therapy after one cycle without treatment. The maximum duration of treatment remains however limited to 3 years from the start of the simulation.

Poorly adherent patients (MPR < 0.8) suffer from a lower treatment efficacy. Poor adherence was associated with a 17% increase in fractures rates (RR = 1.17; 95% confidence interval [CI] 1.09–1.25) [10]. The RRs from the NICE meta-analysis were applicable to the population with adherence of 0.8 or greater. So, for instance, if oral bisphosphonates was assumed to reduce the risk of hip fracture by 29%, then adherent patients would experience a 29% reduction in hip fracture while poorly adherent patients would experience only a 17.1% (0.71 \times 1.167 = 0.829) reduction in hip fracture. Drug costs in the groups of poorly and highly adherent patients were adjusted by the mean MPR of the group. In the full-adherence scenario, drug cost was equal to the MPR of the group of adherent patients (i.e., MPR = 0.8) (see Appendix 2, Table 3, in Supplemental Materials found at doi: 10.1016/j.jval.2012.02.001). Adherent patients from the real-world adherence scenario and patients from the full-adherence scenario were therefore associated with the same drug cost.

**Analyses and simulation**

Patients were stratified into groups according to sex (female/male) and age (55–64, 65–69, 70–74, and 75 + years). They entered into the model at the age of 60, 67, 72, and 80 years for the different age groups, respectively. First-order Monte-Carlo microsimulations (trials) were performed for each scenario, and fractures, costs, and QALYs were recorded over 3 years and over a patient’s lifetime. A single outcome’s value is the sum of the outcomes (i.e., costs and QALYs) from the states traversed by an individual. By simulating patients one by one, a microsimulation model introduces variability between patients that can be reduced by simulating a large number of patients. A total of 200,000 trials were deemed sufficient to guarantee the stability of the results [28]. To enable variability analyses, each model was run 10 times with 200,000 patients.

The potential loss of benefits resulting from poor adherence was first estimated by comparing the outcomes (i.e., number of fractures and QALYs) obtained at real-world adherence levels with those expected with full adherence. The number of fractures resulting from poor adherence in patients from the adherence database was then determined by multiplying the difference between the lifetime number of fractures in the full and real-world adherence scenarios by the number of patients included in the different age and sex groups. The incremental cost-effectiveness ratio (ICER) was calculated between the three adherence scenarios. ICER is defined as the difference in terms of (lifetime) cost between strategies divided by their difference in terms of (lifetime) effectiveness (here measured as QALYs). An ICER represents the incremental cost per one QALY gained. Mean ICER and the 95% CI were calculated for each analysis. Future costs and health effects (QALYs) were discounted by 4% annually according to the Irish guideline for cost-effectiveness research [47].

Sensitivity analyses were performed to assess the impact of assumptions on the results. These include changes in fracture risk, cost and disutility, excess mortality, and assumptions on medication adherence. In particular, other refill gaps and MPR
thresholds were examined. Additional simulations estimated the cost-effectiveness of hypothetical adherence-enhancing interventions according to their cost (marginal and one-time costs) and effect on adherence (improvements between 10% and 50% [21]). Because interventions can be associated with marginal (e.g., monitoring) or one-time (e.g., education program) costs, both aspects were investigated.

Results

Adherence data

In women, persistence rates were 64.3%, 52.7%, and 45.0% after 1, 2, and 3 years, respectively (Table 2). These values were 60.0%, 41.1%, and 29.4% in men. In the subgroup of persistent patients, the probabilities of being highly adherent (MPR ≥ 0.8) were estimated between 82.3% and 93.0%.

Results are sensitive to the refill gap length and to the MPR threshold. So, for example, 56.8%, 64.3%, and 69.0% of women were considered as persistent after 1 year using a 5-, 9-, and 13-week refill gap, respectively. The probability of being highly adherent (MPR greater than or equal to the threshold) was estimated on average at 94.1%, 89.1%, and 75.7% assuming a threshold of 0.7, 0.8, or 0.9 for high adherence, respectively.

Reinitiation rates at 1 year were 25.4% for women and 21.5% for men, with a gap length of 9 weeks. These values were 42.1% and 34.9%, and 16.9% and 14.5% with refill gap periods of 5 and 13 weeks, respectively. Mean MPR in the group of adherent and non-adherent patients ranged from 0.95 to 0.96 and from 0.47 to 0.70, respectively.

Model validation

The model performed well during validation, producing fracture incidence and mortality rates that were similar to the observed data. Under the assumption of no treatment, absolute lifetime risks of hip fracture and of any major osteoporotic fractures (hip, vertebral, or wrist) were estimated, respectively, at 21.3% and 39.6% for a women aged 60 years with the fracture risk of the average population, in the range of estimates reported in the literature [48]. Expected life expectancies were also very similar to empirical data (differences of <0.1 year). Furthermore, tests on model parameters and modeling assumptions (such as the effects of changing the value of some parameters) were consistent with expected conclusions. Model-based projections of prescription drug use were also validated. By using the model, we calculated the percentage of patients on osteoporosis drug therapy at 3 years (including patients who have restarted therapy after stopping). These values were 52.5% and 35.6% for women and men, respectively, consistent with estimates of 53.4% and 34.3%, respectively, from the adherence database. To determine the number of simulations, a varying number of trials (from 10,000 to 500,000) were run 10 times and, as in the case of the Belgian version of the model [28], the distance between the upper and lower limits of the 95% CIs of the ICER of osteoporosis medications compared with no treatment reached a plateau from 200,000 trials.

Societal burden: base-case analysis

The mean lifetime number of hip fractures per patient was 0.49 for the no-treatment scenario, 0.47 for the real-world scenario, and 0.46 for the full-adherence scenario. The equivalent values for any osteoporotic fractures were 1.32, 1.27, and 1.23, respectively (Table 3). Therefore, the lifetime number of hip and all osteoporotic fractures prevented in the case of real-world adherence represent 56.7% (95% CI 56.2%–57.3%) and 56.3% (95% CI 56.0%–56.7%) to that estimated with full-adherence scenario, respectively (Fig. 2). The QALYs gain in the real-world adherence scenario was estimated at 56.0% (95% CI 54.6%–57.5%) to that obtained under full-adherence scenario. When assuming a 3-year time horizon, the number of fractures and the QALYs gain obtained at real-world adherence scenarios represent 65.7% (95% CI 65.9%–65.9%) and 65.4% (95% CI 64.0%–66.9%) to that estimated with the full-adherence scenario, respectively.

Compared with no treatment, real-world adherence scenario was associated with an additional lifetime cost of €266.3 and a 0.023 lifetime QALY gain, giving an ICER of €11,834 per QALY gained (95% CI €11,197–€12,470), as illustrated in Table 3. The full-adherence scenario was associated over lifetime with a lower cost and a higher QALY than the real-world adherence scenario, giving a negative ICER of €–659 per QALY (95% CI €–1488 to €–171). Full adherence is said to be cost-saving compared with real-world adherence.

For the 83,282 patients included in the database, the lifetime number of hip and of all osteoporotic types of fractures due to medication nonadherence was estimated at 1271 (95% CI 1238–1304) and 3340 (95% CI 3295–3386), respectively. These fractures result in a QALY loss of 1470 (95% CI 1398–1544).

Societal burden: sensitivity analyses

As observed in Table 4, the percentage of QALY loss due to poor adherence is substantially greater in men than in women. Other analysis suggests that the burden of adherence was primarily driven by persistence. Full adherence was responsible for 4.5% [{(3340 – 3191)/3340}] of the number of fractures, and 7.8% [{(100 – 56.3) – (100 – 59.7)}/(100 – 56.3)] of the QALY loss, attributable to poor adherence. Definitions of nonadherence (i.e., refill gap period and MPR threshold) also had an impact on the results, while baseline fracture

| Table 2 – Persistence and adherence data in Irish women and men*. |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                          | 6 mo                     | 1 y                      | 1.5 y                    | 2 y                      | 2.5 y                    | 3 y                      |
| **Women**                |                          |                          |                          |                          |                          |                          |
| Nonpersistence           | 26.2%                    | 35.7%                    | 41.9%                    | 47.3%                    | 51.9%                    | 55.0%                    |
| Poor adherence           | 13.1%                    | 7.7%                     | 5.9%                     | 4.7%                     | 4.1%                     | 3.5%                     |
| High adherence           | 60.8%                    | 56.6%                    | 52.2%                    | 48.0%                    | 43.9%                    | 41.5%                    |
| Number of persistent cases | 52,192                   | 42,819                   | 35,925                   | 30,051                   | 24,983                   | 20,781                   |
| **Men**                  |                          |                          |                          |                          |                          |                          |
| Nonpersistence           | 40.0%                    | 51.8%                    | 58.9%                    | 64.0%                    | 68.1%                    | 70.6%                    |
| Poor adherence           | 10.0%                    | 5.3%                     | 3.4%                     | 2.5%                     | 2.3%                     | 2.1%                     |
| High adherence           | 50.0%                    | 43.2%                    | 37.7%                    | 33.5%                    | 29.6%                    | 27.3%                    |
| Number of persistent cases | 7,569                    | 5,557                    | 4,246                    | 3,323                    | 2,567                    | 1,991                    |

* Refill gap period of 9 wk; medication possession ratio of ≥0.8 to define high compliance, <0.8 to define poor adherence.
risk and treatment efficacy markedly affected the number of fractures attributable to poor adherence. Because more patients were good adherers when assuming an MPR threshold of 0.7, this scenario resulted in higher QALY gain and fractures prevented.

### Potential adherence-enhancing interventions

Figure 3 presents the cost-effectiveness of potential adherence-enhancing interventions according to their cost and effect on adherence. So, for example, an intervention to improve adherence and persistence by 25% would result in an ICER of €11,511 per QALY (95% CI 9,238–13,784) and €54,182 per QALY if the intervention cost an additional €50 and €100 per year, respectively. For potential interventions associated with a 50% increase in adherence rates, their cost-effectiveness was estimated at €26,999 per QALY (95% CI €25,034–€28,965) and €56,195 per QALY (95% CI €52,084–€60,166) for additional annual costs of €100 and €150, respectively. In other terms, a program to improve adherence and persistence by 10%, 25%, or 50% would remain cost-effective at a threshold of €45,000 per QALY if it cost a maximum of €119.4, €299.0, and €726.3 annually per patient, respectively.

### Discussion

Poor adherence undermines the potential effectiveness of osteoporosis medications in preventing fractures. By using simulation modeling, we estimated that approximately 50% of the expected benefits of osteoporosis medications were lost because of nonadherence. Moreover, poor adherence resulted in approximately a doubling of the cost per QALY gained from these medications. Sensitivity analysis...
This analysis suggests. A similar analysis was conducted in Belgian women by both persistence and adherence on clinical and economic outcomes in both men and women with varying definitions for nonadherence (MPR threshold and gap lengths). We have also chosen a database that estimates persistence, adherence, and reinitiation rates in the model after discontinuation; the cost of restart therapy in the model after discontinuation; the cost of medications. The cost of interruption, the same adherence level was applied. Such patients may however resume at a less adherent level, but this would require further investigation.

Another potential limitation of this study is that using prescription refill rates may overestimate medication adherence because it assumes that patients take all the dispensed medications, but not necessarily persistence. Prescription refill rates are, however, generally the only way to estimate adherence and represent a reliable and inexpensive way of evaluating persistence and adherence. Another reason for the underestimation of the burden of poor adherence is the lack of inclusion of primary nonadherent patients. This term refers to patients who never fill a prescription. These patients were not included in the database because our study was based on pharmacy records of filled prescriptions. In addition, our manuscript deals primarily with direct costs. Decrease in medication adherence reduces significantly medications effects and subsequently increases the need for surgery. Lack of adherence and the subsequent fracture increase also impact all health care resources utilization including physiotherapy and occupational therapy. Caregiver costs as well as loss of productivity and absenteeism were also shown to be significant in osteoporosis management, and the lack of adherence in osteoporosis medications may potentially result in overutilization of pain medication, which can also be linked to decreased productivity.

Another limitation is that highly adherent patients will achieve reductions in fracture risk based on meta-analysis from published clinical trials. This seems plausible because trials are likely to reflect the highest achievable rate of adherence in actual practice. However, because adherence in all the trials (and not unique to osteoporosis) is not optimal for all the patients, the efficacy from these trials is likely to be reduced to some degree because of nonadherence and nonpersistence. Therefore, we probably underestimated the true underlying risk reduction with therapy. Another limitation is the use of a dichotomous measure for persistence and adherence, which is likely to result in a loss of power between patients who are fully nonadherent and those who are just below the cutoff point for adherence.

Table 4 – Sensitivity analyses on the clinical burden (expressed in % of QALY gain and in number of osteoporotic fractures) of poor adherence with osteoporosis medications.

<table>
<thead>
<tr>
<th>% of QALY gain</th>
<th>Number of fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-case analysis</td>
<td>56.3 (54.5–57.5)</td>
</tr>
<tr>
<td>Women</td>
<td>57.6 (56.2–59.1)</td>
</tr>
<tr>
<td>Men</td>
<td>44.7 (42.6–46.8)</td>
</tr>
<tr>
<td>5-wk refill gap</td>
<td>50.9 (49.1–52.7)</td>
</tr>
<tr>
<td>13-wk refill gap</td>
<td>59.9 (58.2–61.6)</td>
</tr>
<tr>
<td>Full compliance</td>
<td>58.7 (58.2–61.2)</td>
</tr>
<tr>
<td>MPR of 90%</td>
<td>54.7 (53.3–56.1)</td>
</tr>
<tr>
<td>MPR of 70%</td>
<td>58.0 (56.9–59.2)</td>
</tr>
<tr>
<td>Treatment efficacy 20%</td>
<td>58.0 (56.9–59.1)</td>
</tr>
<tr>
<td>Fracture risk 25%</td>
<td>54.5 (52.7–56.3)</td>
</tr>
<tr>
<td>Fracture risk – 25%</td>
<td>57.4 (56.1–58.5)</td>
</tr>
</tbody>
</table>

MPR, medication possession ratio; QALY, quality-adjusted life-year. 1 Percentage of QALY gain for the simulated scenario compared with that obtained with the full-adherence scenario. 2 Under full adherence, 7645 osteoporotic fractures would be prevented. 95% CI are provided in parentheses.

Fig. 3 – 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 gray lines represent the lower and upper limits of the 95% confidence interval. QALY, quality-adjusted life-year.
Finally, like all models, several limitations must be taken into account. The most important are availability of data. Although much of the data used to construct the model were extracted from the Irish data sets, some data were extrapolated from other countries, as was the case for the Belgian model [23]. In particular, the impacts of fractures on health-related quality of life were generally derived from a Swedish study [35]. Although fracture disutility tends to be similar between several countries [34], differences may be present between Irish and Swedish patients. It could be argued that hip fractures are the fracture type considered to be the key driver in the cost-effectiveness of osteoporosis medications [54] and their incidence and costs were estimated from a local database. Potential limitations of the model have been previously extensively discussed [17,23]. In particular, the threshold for adherence remains uncertain because there is no clinically meaningful definition for high adherence. Further studies should reexamine the 0.8 threshold for adherence.

Generalizability of the results to the whole population may also be uncertain because adherence and persistence data were based on a subpopulation in Ireland that is more socially deprived and elderly. We do not, however, expect that adherence and persistence data will substantially differ.

Our analysis may have important clinical and economic implications. First, it suggests that poor adherence can be considered as the critical hurdle to osteoporosis management. Improving adherence is therefore becoming urgent, but it remains a complex issue. Behavioral programs to improve adherence with osteoporosis medications have been initiated, but few interventions were efficacious, and, in absence of clear trends regarding successful intervention techniques can be identified [21]. New formulations and longer dosage regimens have also been recently available, which in principle can help to improve adherence [55]. Less frequent dosing regimens have been frequently associated with better adherence [56,57]. There is a need to conduct additional research with behavioral interventions and to consider the impact of specific pharmacological treatments on medication adherence. Because many determinants of poor adherence have been identified [58,59], understanding patients’ preferences for osteoporosis treatments and involving patients into clinical decision making may certainly be useful in optimizing treatment selection and in improving adherence to therapy. Second, our analysis highlights the importance of integrating medication adherence and persistence in pharmacoeconomic analyses conducted in osteoporosis [26–28,30]. Poor adherence represents a new perspective on health economic assessment in osteoporosis [60], and our study may provide an interesting background for integrating medication adherence and persistence.

In summary, this analysis suggests that poor adherence with osteoporosis medications results in approximately a 50% reduction in the potential benefits observed in clinical trials and a doubling of the cost per QALY gained from these medications. Moreover, depending on their costs and outcomes, programs to improve adherence have the potential to be an efficient use of resources.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at doi: 10.1016/j.jval.2012.02.001 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES


