

The importance of integrating medication adherence into pharmacoeconomic analyses: the example of osteoporosis

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Adherence to medications is poor and suboptimal in many chronic diseases. Nonadherence can reduce treatment effectiveness and can have an impact on healthcare costs. As a consequence, it may alter the cost–effectiveness of drug therapies. This article emphasizes the importance of integrating medication compliance and persistence into pharmacoeconomic evaluations, using osteoporosis as an example. A limited number of studies carried out to date have suggested important economic implications of poor adherence to osteoporosis medications. Therefore, compliance and persistence should be an integral part of clinical studies and pharmacoeconomic analyses in order to estimate the cost–effectiveness of drug therapies in current community practice. Measuring adherence and incorporating it into health economic modeling may, however, pose particular challenges.

KEYWORDS: adherence • compliance • cost–effectiveness • economic • osteoporosis • persistence

Pharmacoeconomic evaluations are increasingly used in healthcare. By comparing costs and consequences of health interventions, economic evaluations can serve as a tool to help decision-makers to efficiently allocate scarce resources. To conduct economic evaluations, researchers often obtain efficacy data from randomized controlled trials (RCTs). Although RCTs have, at least theoretically, high internal validity, they are associated with high levels of adherence compared with those observed in daily practice. The estimates of treatment efficacy and subsequently pharmacoeconomic results may therefore not be generalizable to current community practice. In order to estimate the cost–effectiveness of the intervention/drug in real-life settings, it is important that economic evaluations take adherence into account. Poor compliance and persistence will reduce the cost of the intervention, but at the same time might decrease the side effects and the therapeutic potential of drug therapy in terms of health effects and costs, and can therefore have a substantial impact on the effectiveness and cost–effectiveness of drug therapies [1].

This study aims to highlight the importance of integrating medication adherence into pharmacoeconomic analyses, using osteoporosis

as an example. Poor compliance and persistence are common problems in the treatment of osteoporosis. Approximately 75% of women in whom an oral bisphosphonate – currently the most widely prescribed treatment for osteoporosis – is initiated have been shown to be non-adherent within 1 year and 50% discontinued therapy by this time [2,3]. A few studies carried out to date have suggested important economic implications of poor adherence to osteoporosis medications [4–8].

More specifically, the purposes of this article are: first, to present and illustrate, by a published example including reviews and single studies, the impacts of poor adherence to osteoporosis medications on effectiveness, healthcare costs and cost–effectiveness; second, to review recent economic evaluations that have integrated compliance and persistence; and last, to discuss some important challenges for incorporating compliance and persistence into pharmacoeconomic analyses conducted in osteoporosis.

Definition & measurements

As a wide variety of definitions for medication adherence have been used in the literature, it is important to define the terminology. In line

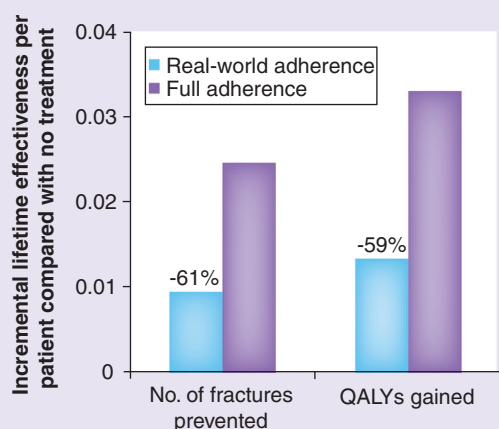


Figure 1. Impact of medication nonadherence on the clinical effectiveness (expressed as number of fractures prevented and quality-adjusted life-years gained) of oral bisphosphonates. Using a simulation model, this study estimated the lifetime effectiveness per patient at real-world adherence levels and full adherence with oral bisphosphonate compared with no treatment. Analysis was conducted in Belgian patients aged 55–85 years, either with a bone mineral density T-score ≤ -2.5 or a prevalent vertebral fracture at baseline. Medication nonadherence decreased by 61 and 59% for the number of fractures prevented and the QALY gain of oral bisphosphonates compared with the full adherence scenario, respectively. QALY: Quality-adjusted life-year. Data taken from [4].

with the definitions issued by an expert consensus group on osteoporosis [9], medication adherence is used as a general term to cover medication compliance and persistence. Medication compliance may be defined as “the extent to which a patient acts in accordance with the prescribed interval, dose and dosing of regimen” and medication persistence as “the length of time from initiation to discontinuation of therapy” [10].

Medication compliance is typically expressed as the percentage of prescribed doses taken in relation to the study period, often termed the medication possession ratio (MPR). Studies conducted on osteoporosis have estimated the mean MPR over a period of time (typically 1 year) and/or the probabilities of patients being highly or poorly compliant. A threshold of 80% has been most commonly used to define high compliance with osteoporosis treatments [11]. However, the definition of ‘good compliance’ is arbitrary and difficult to evaluate. An empirical calculation of an optimal threshold for predicting fracture risk has been estimated at 68% [12].

Persistence is measured as the number of days on therapy or as a dichotomous variable (persistent or not) as to whether a patient continued therapy beyond a certain elapsed time period (e.g., 12 months). A threshold regarding discontinuation period has to be defined for measuring persistence. For daily or weekly treatment, a refill gap of 1 month is commonly considered to define nonpersistence [13], but, as for MPR thresholds, there are no standardized definitions for nonpersistence. Gap lengths for

treatments with longer dosing intervals are less well defined, although a working group recently discussed the notion that stopping treatment for 2 months may be a suitable definition for a monthly treatment, and a delay of more than 3 months in the case of yearly injections [13]. The operational definitions to measure compliance and persistence could therefore differ between studies and may impact the results.

Medication compliance and persistence can be assessed using direct or indirect methods. Direct assessment methods (e.g., observation, serum drug concentration and biochemical analysis) are more accurate but are more costly and often impractical [14]. Indirect methods (e.g., retrospective prescription claims database) often constitute the only available source to assess adherence and an inexpensive way of collecting adherence [15]. Most studies assessing medication adherence have used pharmacy prescription refill records. This method, however, lacks the details of daily dosing (e.g., missing doses or wrong timing) and may underestimate medication nonadherence and, especially, noncompliance.

Impact of poor adherence on antifracture effectiveness

Poor adherence reduces the effectiveness of osteoporosis treatment, resulting in lower bone mineral density gains and subsequently higher fractures rates [16]. Two meta-analyses were recently performed to assess the fracture risk among patients who were noncompliant versus those who were compliant to therapy for osteoporosis [17,18]. First, a meta-analysis of six articles, including 171,063 patients, suggested that the risk of fractures was 46% higher in noncompliant patients (MPR <80%) with bisphosphonate therapy compared with compliant patients [18]. The increased fracture risk in noncompliant patients was lower for nonvertebral (16%) and hip (28%) than for clinical vertebral fractures (43%). In another meta-analysis, encompassing 113,376 patients from eight studies, of which the majority were retrospective database analyses considering the effect of adherence to bisphosphonate therapy, fracture risk increased by approximately 30% in noncompliant patients (MPR <80%) compared with compliant patients [17].

Most of these studies have suggested a nonlinear relationship between MPR and fracture risk [11]. For example, a large US database showed no treatment benefit for compliance levels defined by an MPR <50% and then an exponential decrease of fractures rates as compliance increased [19]. Similarly, a German study observed no risk benefit with compliance levels of less than 60% [20]. Elsewhere, however, a linear relationship was observed between MPR (expressed as a continuous variable) and the probability of hip fractures [21]. Each incremental decrease of 1% in compliance resulted in an increase in the risk of hip fracture by 0.4% [21].

Nonpersistent patients also reported higher fracture rates compared with persistent patients. A meta-analysis including 57,334 patients from five studies showed that nonpersistence increases the risk of all fractures by 30–40% versus persistence [18]. A recent Swedish observational study also showed that the 3-year fracture incidence was related to time on treatment with osteoporosis medications [22]. Consistent with RCTs, this study shows that, in real-life settings, at least 6 months of treatment with oral

bisphosphonates can reduce fracture incidence [22,23]. No treatment effect could therefore be assumed for patients receiving drug therapy for less than 6 months.

The magnitude of the effects of medication adherence should be interpreted with some caution [24]. A limitation to the observational studies is the concern surrounding bias due to the 'healthy adherer effect', which could lead to an overestimation of medication benefits. While the reduced effectiveness observed in noncompliant and nonpersistent patients may be due to a true biological effect, it may also be at least partly caused by confounding factors due to differences between the types of patients who remain adherent versus those becoming nonadherent. In the Women's Health Initiative's study [24], adherence to placebo significantly reduced the risk of hip fracture by 50%. However, these results are not supported by another study that shows no evidence of healthy adherer bias in a frail cohort of seniors [25] and further exploration of the healthy adherer effect would be required in osteoporosis.

Acknowledging this potential limitation, poor adherence may be responsible for a large difference between efficacy and clinical effectiveness. The consequences of poor adherence on the clinical effectiveness at a population level have been shown to be significant in many countries [4,6,7,26]. An example of the impact of medication adherence on effectiveness is provided in **FIGURE 1**. Using Belgian data on persistence and compliance to alendronate, an oral bisphosphonate [21], and simulation modeling [27], this study compared the clinical and economic outcomes obtained at real-world adherence levels with those expected with full adherence over 3 years [4]. Outcomes were expressed as the number of hip fractures and in quality-adjusted life-years (QALYs), which is an attractive outcome measurement for cost-effectiveness analyses that takes into account reductions in both morbidity and mortality. The numbers of hip fractures prevented were 0.0095 and 0.0247 for the real-world and full adherence scenarios, respectively [4]. Therefore, the number of hip fractures prevented in the case of real-world adherence represents only 38.5% of that estimated with full adherence. The gain in QALYs in the real-world adherence scenario was estimated at 40.6% of that obtained under the full adherence scenario. More than half of the potential clinical benefits of oral bisphosphonates in patients with osteoporosis are therefore expected to be lost owing to poor compliance and failure to persist with treatment. Sensitivity analysis has shown that the effect of nonadherence on clinical effectiveness was primarily driven by issues of nonpersistence, with more than 90% of the clinical burden of poor adherence resulting from nonpersistence [4].

Impact of poor adherence on healthcare costs

Poor adherence will work in two opposite directions on healthcare resources [1]. Nonadherence reduces the cost of therapy but increases healthcare costs associated with the condition being treated as a result of reducing clinical effectiveness. The overall impact of nonadherence on healthcare costs will be primarily dependent on the risk of the population. The impact of poor adherence on therapy cost will be the same across different

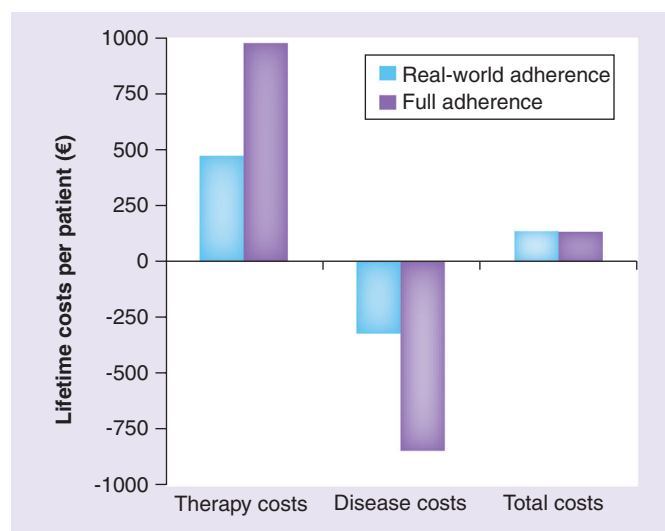


Figure 2. Impact of medication nonadherence on aggregated and disaggregated (drug and disease) healthcare costs. Using a simulation model, this study estimated the aggregated and disaggregated costs associated with oral bisphosphonate therapy at real-world adherence and full adherence levels in comparison with no treatment. Analysis was conducted in Belgian patients aged 55–85 years either with a bone mineral density T-score ≤ -2.5 or a prevalent vertebral fracture at baseline. Aggregated costs (total costs) include the costs of therapy (drug and monitoring costs) and fracture-related costs (disease costs). Data taken from [4].

populations, but the number of fractures avoided and the corresponding disease-related costs will increase as the fracture risk of the population increases. It could therefore be possible, in high-risk populations, for the averted costs of treating the additional osteoporotic fractures resulting from noncompliance to exceed the cost of the additional therapy stemming from the improved compliance.

In our example including women between 55 and 85 years of age with either a bone mineral density T-score below -2.5 or a prevalent vertebral fracture, the full and the real-world adherence scenarios had approximately the same total cost (**FIGURE 2**) [4], meaning that the additional costs from treating nonadherent patients to full adherence are approximately equal to the averted fracture costs resulting from improved adherence. Of course, the change in drug and nondrug costs is a function of both persistence and compliance [1,28].

Impact of poor adherence on cost-effectiveness

Given that compliance and persistence affect both health outcomes and costs, these concepts should be included to accurately estimate the cost-effectiveness of drug therapies. In our example using observational data (**FIGURE 3**), the impact of medication adherence on cost-effectiveness is substantial. The incremental cost per QALY gained of oral bisphosphonates compared with no treatment was estimated at €10,279 and €3909 at real-world and full (assumed) adherence levels, respectively [4]. In this example, poor adherence therefore results

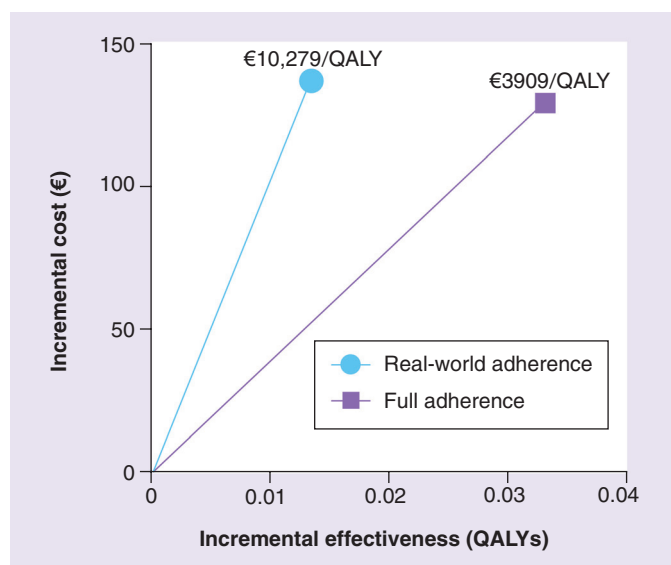


Figure 3. Impact of medication nonadherence on the cost-effectiveness (expressed as cost in euros per quality-adjusted life-year gained) of oral bisphosphonates compared with no treatment. This figure (called the 'cost-effectiveness plane') presents the incremental effectiveness and costs of oral bisphosphonates compared with no treatment at real-world and full adherence levels. The incremental cost-effectiveness ratio is represented by the slope of the line from the origin. The analysis was conducted in Belgian patients aged 55–85 years either with a bone mineral density T-score ≤ -2.5 or a prevalent vertebral fracture at baseline. QALY: Quality-adjusted life-year. Data taken from [4].

in around a doubling of the cost-effectiveness from these medications. It means that for example, with a budget of €20,000, treatment with oral bisphosphonates could save 1.95 life-years in perfect health at real-world adherence levels while, at full adherence, treatment could preserve 5.12 life-years in perfect health. The studies addressing compliance and persistence have shown that both aspects of adherence were important drivers of cost-effectiveness [5].

Approaches to integrate nonpersistence & noncompliance into economic evaluations

In recent years, several studies have attempted to integrate medication compliance and/or persistence into pharmacoeconomic evaluations conducted in osteoporosis. As compliance and persistence are two different constructs, both concepts should ideally be separated. In order to avoid blurring the distinction between compliance and persistence, it is also important that compliance is defined in the subgroup of persistent patients. Studies generally provide assumptions with respect to persistence but generally oversimplify the contribution of compliance. Below, we describe some of the approaches to integrate persistence and compliance.

In the first economic models of persistence, including one by the National Institute for Health and Clinical Excellence in the UK, it was assumed that some patients completed the full 5-year

course and the remaining (i.e., nonpersistent) patients received no treatment effect but 3 months of costs [29,30]. A value of 50% nonpersistent patients was selected in the base case. Patients who discontinue therapy early may have a marked impact on cost-effectiveness, as they receive drug costs but have no treatment effect. For example, the incremental cost-effectiveness ratio of generic alendronate in UK women with bone mineral density T-scores equal to -2.5 and no prior fracture was estimated at GBP£3163, £3709 and £4914 per QALY gained when assuming 30, 50 and 70% of nonpersistent patients, respectively [29]. However, in real-life settings, patients are likely to discontinue at any time and not only after 3 months [30].

More recent studies have therefore incorporated the possibility that patients can be at risk of discontinuation over the whole period of time [30–32]. Every patient is therefore considered to have a risk of stopping therapy in every cycle, based on observational adherence studies. For patients stopping therapy in each cycle, it is frequently assumed, first, that they receive no further treatment during the remaining modeling time and, second, that offset time (i.e., effect of treatment after stopping therapy) is similar to the duration of therapy. Although the latter notion seems reasonable, assumptions made regarding the offset time may have a large impact on the results [30]. Limited data available from extension studies of RCTs have suggested that the discontinuation of oral bisphosphonate resulted in the gradual loss of its effects [33] and was found up to 7 years after treatment discontinuation [34]. Further research would, however, be needed to understand offset action of new anti-osteoporosis medications. The first assumption may be more critical as approximately a third of patients were shown to restart treatment within 6 months after discontinuation [35,36]. How these patients change the cost-effectiveness is, however, unclear, and their inclusion in modeling may be difficult as the effectiveness of oral bisphosphonates used in an interrupted way is largely unknown.

Studies have also attempted to include medication compliance. Most studies assumed medication costs and fracture reduction efficacy to be proportional to compliance [27,37,38]. This approach may, however, be inappropriate since the relationship between MPR and fracture risk has been shown in most studies to be nonlinear [11].

Ström *et al.* used another approach to model compliance. They reduced treatment efficacy by a proportional factor of the optimal antifracture effect [30]. The authors suggested a 20% reduction of treatment benefit due to noncompliance in the base case, based on expert opinion. Noncompliant patients therefore deteriorated the cost-effectiveness because they received less benefit but had the same cost.

Hilgsmann *et al.* estimated the relative risks of fracture according to MPR [5]. The effectiveness from clinical trials was applicable to the population with an MPR value equal to 80% and fracture reduction efficacy at other MPR values was estimated based on the relationship between compliance and fracture risk [19,21]. For generic oral bisphosphonates, the incremental cost-effectiveness ratio was estimated at €4871, £11,985 and €30,181 for 100, 80 and 60% compliance, respectively.

Hilgsmann *et al.* suggest an original methodology including real-world estimates for compliance with oral bisphosphonates [4,8,34]. Persistent patients were classified as compliant (MPR $\geq 80\%$) and poorly compliant (MPR $< 80\%$). The probabilities of being compliant or not were derived for any given year and poorly compliant patients were assumed to be associated with an increased risk of fractures [21,39]. Drug costs were also related to the mean MPR of the patients.

Using this approach, the cost–effectiveness of denosumab compared with generic alendronate (an oral bisphosphonate) was estimated in the treatment of postmenopausal osteoporotic women [32], using real-world adherence data for alendronate and accepting an improved persistence for the 6-month subcutaneous injection of denosumab based on the results of an open-label study [40]. A shorter offset time of the antifracture effect after stopping treatment was assumed for denosumab compared with that selected for alendronate. In the base-case analysis, the cost per QALY gained for denosumab compared with generic alendronate was estimated at €22,220 in women 70 years of age with bone mineral density T-scores of -2.5 or less. When assuming a 25% higher adherence for oral bisphosphonates, the incremental cost–effectiveness ratio increased to €41,759. Medication adherence can therefore be considered as a key driver of the results. If adherence had not been included, the incremental cost–effectiveness ratio of denosumab compared with oral bisphosphonates would be less favorable. When comparing drugs with potential differences in medication compliance and persistence, the lack of inclusion of these concepts could bias the results and lead to suboptimal allocation of resources.

Economic value of adherence-enhancing interventions

In recent years, there has been an increasing interest in determining the effects of programs to improve adherence to osteoporosis medications. Several studies have investigated the effects of changing the dosing of regimens of bisphosphonates and/or improvements of compliance and persistence on the number of fractures prevented [6,41–44]. Some studies also estimated the economic value (in terms of cost per QALY gained) of improving medication compliance and persistence [26,30,45]. These studies did not assess the cost–effectiveness of a specific program but estimated the cost–effectiveness of hypothetical interventions. As mentioned above, depending on the baseline risk for fractures, such interventions can, but will not necessarily be, cost effective.

Results of these studies suggest that interventions to improve adherence may likely confer cost–effectiveness benefits. So, for example, a hypothetical intervention with a one-time cost of US\$250 and a reduction in discontinuation by 30% had an incremental cost per QALY gained of US\$29,571 in American women aged 65 years starting bisphosphonates [26]. Other studies [4,31,46], reported in TABLE 1, estimated the maximum amount per year that would be cost effective to spend on interventions

Table 1. Maximum cost per year for an adherence-enhancing intervention to be considered cost effective.

Adherence improvement (%)	Maximum cost per year		
	Sweden, 2009 [30] [†]	Belgium, 2010 [4] [‡]	Ireland, 2012 [45] [‡]
10	€225	€73	€119
25 (30 for Sweden)	€676	€149	€299
50	€1130	€239	€726

[†]Cost–effectiveness threshold of €60,000 per quality-adjusted life-year gained.

[‡]Cost–effectiveness threshold of €45,000 per quality-adjusted life-year gained.

to improve medication adherence, depending on the level of improvement (between 10 and 50%).

Challenges for integrating compliance & persistence into pharmacoeconomic evaluations

Medication persistence and compliance are important drivers of cost–effectiveness analyses conducted in osteoporosis and should therefore be incorporated into pharmacoeconomic analyses. Measuring adherence and incorporating it into health economic modeling may, however, pose particular challenges. A number of avenues for further research have recently been identified [13]. First, it is probably necessary to have better (and standardized) definitions for compliance thresholds and for gap lengths for non-persistence. This is particularly important for new osteoporotic treatments with different dosing regimens. Persistence data seem to be highly sensitive to gap length, which remains particularly uncertain for longer dosing regimens. Improvements in the measurement of compliance and persistence are also required. The development and validation of tools to evaluate adherence (including missing doses and wrong timing) to osteoporosis medications would be useful [47]. Patient-related outcomes from validated questionnaires may provide robust complementary alternatives to medico-administrative database analyses, especially for compliance measurement.

Second, given the large difference between efficacy and effectiveness, improvements in data collection, preferably in real-life settings, are expected. Using local and treatment-specific data are also important. Currently, the majority of studies have considered the effect of adherence to oral bisphosphonate therapies. Further work is expected to assess compliance and persistence with recent osteoporosis medications with longer dosing regimens. There is also a need to conduct studies to assess efficacy and effectiveness according to types and levels of compliance. Retrieving efficacy data from RCTs for high compliance, as is currently frequently done, may be incorrect because compliance in the trials is not optimal for all patients. The efficacy from these trials is likely to be reduced to some degree because of noncompliance and nonpersistence. Therefore, using efficacy data from RCTs for high compliance probably underestimates the true underlying risk reduction with therapy. Clinical results should therefore also be related to the doses taken and not an assumed 100% persistence and compliance [46]. Although compliance and persistence should be better reported in clinical trials, data on compliance and

relation to effectiveness would ideally be derived from registers or observational studies. Additional insight into variables associated with noncompliance (such as age, first or second fracture, multimедication or comorbidity) would also be valuable. Many factors (such as the presence of comorbidities) are associated with medication adherence [48] and may therefore have an impact on the economic consequences of nonadherence. The effect of these factors should be further investigated.

Finally, in parallel with improvements in the collection of data, further work on methods to incorporate medication compliance and persistence into economic evaluations is also required. This should consider the inclusion of patients who restart therapy after discontinuation and better estimates of the true cost for compliant and noncompliant patients. Using microsimulation models, it would also be possible to integrate the impact of events (such as prior fractures or treatment discontinuation) on compliance and persistence. Modeling compliance and persistence as continuous, rather than dichotomous, variables could also improve the power of the analysis. Performing sensitivity analyses on adherence data and assumptions is also recommended.

Expert commentary

A total of 10 years ago, Hughes *et al.* [49] and Cleemput *et al.* [50] reviewed the literature on the economic impact of noncompliance and identified a need for more and better research. In 2007 and 2009, Hughes *et al.* [1] and Rosen *et al.* [51], respectively, provided updates of the reviews, suggesting that the work is still sparse, and that the limited evidence available has methodological limitations.

In osteoporosis, the incorporation of medication compliance and persistence into pharmacoeconomic evaluations is relatively recent. Most studies recognize the importance of incorporating adherence into health economic models of osteoporosis [5,13,30]. Despite this, these concepts are not yet routinely included. Moreover, when adherence is included, a lack of methodological rigor and consistency in definitions may reduce the impact of medication nonadherence. Few studies have included both persistence and compliance aspects of treatment adherence. However, it should be noted that substantial improvements have been made in some recent studies. As discussed in this paper, the incorporation of medication compliance and persistence in pharmacoeconomic evaluations may be difficult and challenging, and also depends on

data availability. Further research is required and should include the development of appropriate methodology and standards [1].

The importance of integrating medication compliance and persistence into pharmacoeconomic analyses is evident in osteoporosis, but also extends beyond this disease area. Previous studies have shown that noncompliance and nonpersistence have a substantial economic impact in patients with hypertension [52], diabetes mellitus [53,54] or renal transplantation [55]. Health economic modelers should therefore consider the possible impact of nonadherence in all economic evaluations of drug or lifestyle interventions.

Five-year view

Medication compliance and persistence represents a new perspective in health technology assessment of osteoporosis [13]. It is our belief that, over the next 5 years, there will be an increase in the health economic papers incorporating medication compliance and persistence. This will be in line with the collection of additional adherence data. Moreover, as strategies to improve compliance and persistence may confer clinical and cost-effectiveness benefits, we would expect research on the effectiveness and cost-effectiveness of such programs.

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Key issues

- Medication noncompliance and nonpersistence reduce treatment effectiveness, impact on healthcare costs and may therefore alter the cost-effectiveness of drug therapies.
- Several studies carried out to date have suggested important economic implications of poor compliance and persistence with osteoporosis medications.
- Compliance and persistence should be an integral part of clinical (observational) studies and pharmacoeconomic analyses in order to estimate the cost-effectiveness of drug therapies in current community practice.
- Including adherence and incorporating it into health economic modeling may be challenging.
- Depending on their costs and effects, interventions to improve compliance and persistence with osteoporosis medications may confer cost-effective benefits.
- The cost-effectiveness of specific adherence-enhancing interventions should be explored.

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