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ORIGINAL ARTICLE

Incorporating adherence into health economic modelling of osteoporosis

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Abstract
Summary Osteoporosis medications are seldom taken according to the recommendations of health-care providers. A theoretical model was constructed to investigate the variables of drug adherence that affect the cost-effectiveness of drugs, using osteoporosis treatment as a model. Important variables were the magnitude of drug effect, drug price, and fracture-related costs.
Introduction Adherence to anti-fracture medication is far from optimal and poses a challenge in osteoporosis management. The objectives of this study were to develop a model that could address adherence and identify the important drivers of cost-effectiveness.
Methods An individual state transition model was constructed to compare two theoretical medications, one of which conferred optimal adherence and was 50% more costly. Adherence was divided into persistence and compliance. Partial compliance was assumed to be associated with a 20% loss of anti-fracture effect. Non-persistent patients had an offset time as long as their time on medication, to a maximum of 5 years.
Results The potentially important drivers of cost-effectiveness include reduced drug effectiveness due to poor compliance, offset time, fracture risk, anti-fracture drug effect, and drug price. Optimal adherence was associated with fewer osteoporotic fractures, and the impact was more evident among those with prior fractures. However, the health benefits of adherence were often partially offset by increased intervention costs associated with the improved drug-taking behaviour.
Conclusions High adherence is likely to be associated with added value for health-care systems, but should be used with care as a central health economic argument.

Keywords Compliance · Cost-effectiveness · Fracture · Model · Osteoporosis

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Introduction

Non-adherence may be manifest as under- or over-medication, irregular taking of medication (even though the total dosage is correct), discontinuation of treatment, or failure to start taking the medication when recommended by the health-care provider. Adherence is, therefore, intuitively important to achieve some, if not all, of the benefits of a drug. Many studies show that drug adherence is often suboptimal [1], especially in chronic conditions, and presents a serious problem for health care. Adherence in the setting of osteoporosis has been shown to be just as problematic, if not worse, than that in other chronic diseases [2–4]. Osteoporosis is asymptomatic until a fracture has occurred, which may partially explain the low adherence to therapy [5].

Economic evaluations based on modelling are commonly used to compare alternative treatment strategies in osteoporosis, to support decision-makers and to inform treatment guidelines [6–10]. The estimates of treatment effect in economic evaluation are usually based on the efficacy results from randomised clinical trials (RCTs), and the efficacy observed therefore incorporates the adherence of the trial population. Whereas RCTs remain the gold standard for comparing alternative treatments, the high internal validity required to demonstrate efficacy comes at the expense of external validity. The results of such trials may therefore generalise poorly to clinical practice [11, 12]. Consequently, the benefits of treatments that offer better adherence in the real-world setting may be underestimated in cost-effectiveness models if the comparisons are based on clinical trial data alone.

Many health economic models have been developed to evaluate osteoporosis therapies; however, adherence is seldom included in these models. It is important to understand the effects of adherence on the cost-effectiveness ratio of treatments in order to accurately compare the cost-effectiveness of newer treatments, drug delivery methods, and dosing regimens. It is still unclear how adherence should be modelled in economic assessments and which data elements are needed to show the consequences of introducing therapies that improve drug adherence and thus the increased value to patients and health-care systems. The emergence of new treatment options, such as oral, subcutaneous, or intravenous medications that are administered with longer dosing intervals, is likely to raise questions about how adherence should be modelled.

This study had two main objectives:

1. To develop a modelling framework that incorporates variables associated with adherence
2. To identify the important drivers of cost-effectiveness to inform future studies of adherence in osteoporosis

Materials and methods

Defining adherence

There are a variety of definitions of adherence in the literature. A distinction should be made between how long the drug is taken and the proximity of the regimen to the treatment recommendations. For the sake of clarity, the following definitions were used:

- Adherence: a general term encompassing all aspects of persistence, compliance, and primary non-adherence
- Persistence: duration of therapy. Persistence can be expressed as the number of days until discontinuation of the proportion of the cohort still on mediation after a give time
- Compliance: proximity to the recommendations of optimal treatment. This includes how long a drug is taken and can be simplified as the number of doses taken, divided by the number of prescribed doses during a defined period. The term compliance also includes other aspects that impact outcomes, such as if a drug should be taken with or without food, the time of day it should be taken, whether doses are taken to compensate for forgotten doses, drug vacations, pill dumping etc.
- Primary non-adherence: if patients are prescribed a drug and never fill the prescription they are termed a primary non-adherent.

The model

The model used (Fig. 1) was an individual state transition model constructed with TreeAgeis® software. This model was selected instead of a cohort model because calculations were dependent on knowledge of when individual patients dropped out of treatment. The cycle length was 6 months, and all patients were followed from the start of treatment in the base case, at age 70 years, until the age of 100 years or death. All patients began in the *well* state and during each cycle patients had a probability of having a fracture, remaining healthy, or dying. If a fracture occurred, the patient moved to the *hip fracture*, *spine fracture* or *wrist fracture* health state, depending on the site of fracture. After 6 months, the patient could sustain a new fracture, move to the *post-fracture* state, or die. Wrist fracture was assumed

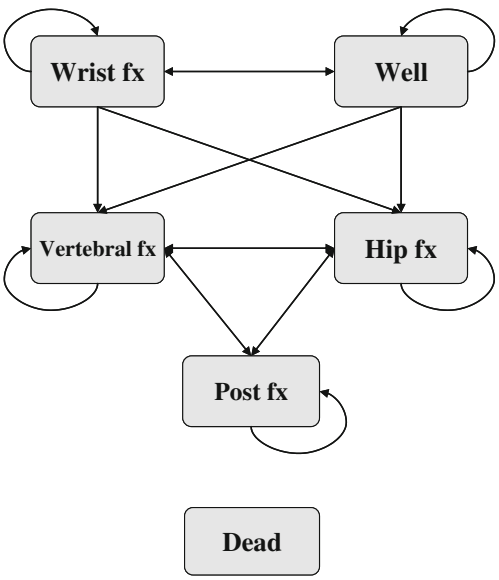

Fig. 1 Structure of the individual state transition model (arrows to dead were excluded for simplicity)

to have an impact on costs and morbidity only in the first year after fracture. Thus, after two 6-month cycles with costs and loss of quality of life (QoL), wrist fracture patients moved back to the *well* health state unless another fracture had occurred. Patients who experienced a hip or vertebral fracture moved to the *post-fracture* state and could remain in that state, have another vertebral or hip fracture, or die. If a patient sustained multiple fractures at different sites during simulations, the cost and QoL loss from the fracture associated with the most severe consequences (high costs and low QoL) were used. A total of 30,000 first-order simulation trials were deemed sufficient to reach stability in the incremental cost-effectiveness ratio (ICER).

Modelling compliance and persistence

The model investigated the cost-effectiveness of two different treatment alternatives with different adherence profiles (i.e. *full adherence* compared with *partial adherence*). Patients in the *full adherence arm* stayed on the treatment for as long as it was intended, and received the full anti-fracture effect that a fully compliant patient would be expected to have. In the *partial adherence arm*, patients were at risk of dropping out of treatment and also had, due to an assumption of poor compliance, a *fraction of the benefit* (FOB) that a fully compliant patient would have. A third arm, simulating a no treatment alternative (with an intake of calcium and vitamin D), was also modelled.

Persistence

In the partial adherence arm of the model, every patient in every cycle had a defined chance of dropping out of treatment and thus did not receive the same anti-fracture benefit as did a persistent patient. In the base case, patients were assumed to be at risk of dropping out during the first 3 years. Thereafter, persistence remained stable until treatment was stopped (i.e. 5 years). This assumption was based on long-term studies indicating that drop-out rates are highest shortly after the initiation of treatment, after which drop-out rates plateau and remain stable for 5 or more years [4, 13]. The risk of dropping out within the first 3 years was estimated from persistence data obtained in a large automated US health-care claims database previously described by Weycker et al. [14]. The persistence rates were based on composite estimates of patients taking bisphosphonates daily, bisphosphonates weekly, or estrogen or raloxifene.

Evaluations of persistence should take into account the fact that persistence is imperfect in RCTs and that fracture risk reductions are estimated from such a population. Most large clinical trials indicate that at least 80% of the patients are on medication at the end of the trial [15]. In this study, no adjustments were made to account for suboptimal adherence in RCTs in the full adherence arm because our model was used in a conceptual context, rather than to reproduce a clinical trial.

If a patient dropped out during the first 6 months, no effect of treatment was assumed, but initial costs (physician's visits and BMD measurements) and 3 months of drug costs were incurred. The proportion of patients that remained on treatment and the corresponding biannual incidence of dropping out are shown in Fig. 2. The drop-out incidence is likely to differ in other parts of the world, and different drop-out rates were therefore explored in a separate analysis.

Compliance

Compliance is defined as how well a patient follows the recommendations for optimal drug treatment. From a modelling perspective, however, that information is irrelevant without knowledge of how compliance is related to fracture risk. Studies investigating the link between fracture risk and refill compliance, as estimated from the medical possession ratio (MPR) [4, 16, 17] suggest that differences in fracture rates between compliant and partially compliant patients range between 16% and 44%. However, non-compliant patients have higher co-morbidity rates, are more frail, and have higher health-care expenditure than do compliant patients [4, 18], and fracture rates are higher in non-compliant patients taking placebo [18]. The MPR estimates are seldom controlled for clinical risk factors, such as smoking, diet, lack of physical exercise, BMD, excess alcohol intake or propensity of falling [19]. Further, MPR should only be estimated in persistent patients since otherwise it will reflect a mixture of both persistence and compliance.

Due to these difficulties in directly linking compliance to fracture rates, poor compliance was modelled as a FOB that ranged from 0 to 100%. FOB refers to treatment benefit and

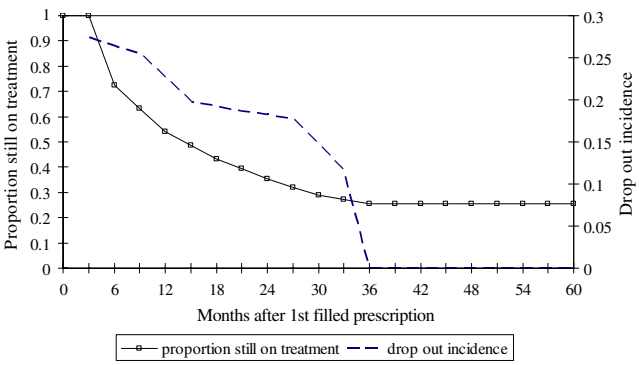

Fig. 2 Proportion of patients still on treatment and the corresponding biannual drop-out incidence used in the model. Incidence is shown as the proportion dropping out at each time point

does not affect the cost of intervention. FOB was the proportion of the optimal anti-fracture effect that a population derived from treatment. In the absence of empirical data, a FOB of 80% was used in the base case. For example, a drug that reduced fracture risk by 50% in a fully compliant population would reduce the risk by 40% in a persistent but partially compliant patient (i.e. 0.5*0.8=0.4).

Primary non-adherence

Primary non-adherence was set to 4% in the base case, based on a study by Ekedahl and Mansson [20], which investigated filled prescriptions at 21 pharmacies in Sweden. The study found that 4% of 70-year-old patients never filled their prescriptions when musculoskeletal drugs were prescribed and were classified as primary non-adherent patients. Primary non-adherent patients were assumed to incur the cost of once physician visit (€100) and one BMD measurement (€100).

Intervention length and offset of treatment effect after discontinuation

The modelled intervention is shown in Fig. 3. In the base case, the maximum duration of drug use (X_1) was set to 5 years. The remaining fracture risk reduction after stopping treatment is not known, but it is usually assumed that the anti-fracture effect continues for a period of time [21]. Offset time was assumed to be 5 years, which has been a commonly used assumption about the treatment effect in previous health economic evaluations of osteoporotic treatments [6, 22, 23]. During this "offset time" (X_2), the fracture risk reduction was assumed to decline linearly to zero. Thus, an intervention in a persistent population had an effect for 10 (5+5) years in the base case. In the partial adherence arm, the offset time was assumed to be as long as the time the patient took the drug; thus, the maximum offset time was also 5 years. An exception to this assumption applied to patients who dropped out during the first 6 months of treatment and therefore received no treatment effect. Two additional scenarios were investigated in sensitivity analyses: one where the offset time was 5 years irrespective of the time of dropping out and one where an offset time of zero was assumed (i.e. there was no residual benefit after stopping treatment).

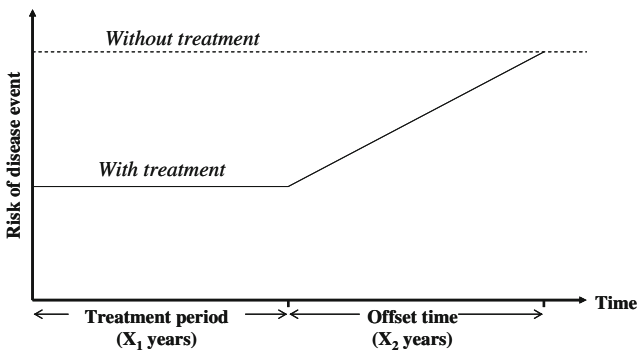

Fig. 3 Effect of intervention

Onset time of anti-fracture effect

The duration of time treatment is needed to reduce fracture risk to the levels reported in RCTs is uncertain. This was termed "onset time", and was defined as the time on treatment necessary to receive the full treatment effect. Some RCTs show that the anti-fracture effect is highest during the first year of treatment, which indicates that onset time is minimal [24, 25]. In the base case, the anti-fracture benefit was assumed to start immediately. A 1-year onset time for treatment effect was explored in a sensitivity analysis. In this scenario, a drug with 50% risk reduction was assumed to reduce fracture risk by 25% after 6 months and then reach its full effect (50%) at 1 year.

Data used to populate the model

The analysis was done from a societal perspective, including health-care costs, costs of informal care, and loss of productivity. Mortality costs were not included in the analysis. All costs were in year 2005 values, and are given in euros. Swedish costs were converted using the average exchange rate (9.26 Swedish krona [SEK]/€ for the year 2005. When needed, the costs were inflated using the Consumer Price Index from *Statistics Sweden* [26]. A yearly discount rate of 3% was used for both costs and effects.

Risk in the population and relative risk of fracture

The age-specific risks of hip, vertebral and wrist fractures for Swedish females used in the model were taken from a population-based study from Malmö, Sweden [27]. To estimate the risk after the age of 89 years, logistic regressions were fitted to the observational data. Fracture risks from the general population were adjusted to reflect the increased fracture risk in the target patient group. The relative risk of fracture of patient groups compared with the risk in the general population was calculated from the BMD and the prevalence of vertebral fractures in the patient groups by methods described previously [10, 28, 29].

The cost of fractures

Costs of a fracture (Table 1) were divided into acute costs, which occurred the first year following the fracture, and

Table 1 Cost of fractures (€)

	Age (years)			
	50–64	65–74	75–84	85+
0–6 months				
Hip fracture	9,685	9,957	9,254	9,958
Vertebral fracture	1,966	4,150	4,150	4,150
Wrist fracture	2,090	1,891	1,891	1,891
7–12 months				
Hip fracture	2,073	884	1,908	3,038
Vertebral fracture	711	2,796	2,796	2,796
Wrist fracture	299	507	507	507

[30, 50, 51] and the Swedish inpatient register

long-term costs, which persisted several years after the fracture or even for the rest of the patient's life. Direct and indirect fracture costs in Sweden during the first year after a hip, clinical vertebral or wrist fracture were derived from the costs and quality of life related to osteoporosis fractures in Sweden (KOFOR) database [30] with the following adjustments to fit the model:

- Costs were calculated for 0–6 months and 7–12 months respectively to fit the cycle length in the model [30].
- 20% of patients with clinical vertebral fractures were assumed to require hospitalisation, based on data from the Swedish inpatient register and population fracture incidence [27], which is more representative of the rate of hospitalisation than the sample of vertebral fracture patients in the KOFOR database [30].
- Costs of hip and vertebral fractures were adjusted downwards because some fracture patients would have been institutionalised at the time of fracture, or would have died shortly after the fracture, and would therefore not incur the same costs [30, 31].

Hip fracture costs after the first year were based on the age-specific proportion of patients [32] who lived at home before the fracture, but then resided in nursing homes 1 year after the fracture (Table 2). These patients were assumed to remain in a nursing home for the rest of their lives [6], at a daily cost of €173 [33]. If a patient sustained a second hip fracture, the proportion going to long-term care (LTC) was dependent on the patient's age at the time of the second fracture. Wrist and vertebral fractures were assumed to incur costs only in the first year after fracture.

The cost of intervention

All patients assigned to treatment had one initial BMD measurement and one initial physician visit during the first year, and then incurred 0.25 BMD tests and 0.5 physician visits every cycle on treatment during the second and subsequent years (i.e. one physician visit every year and one BMD measurement every second year). The drug price in the partial adherence arm was chosen to approximate the cost of oral fracture prevention treatment in Sweden, and was set to €400/year. Together with the costs of physician visits (€100/visit) and the cost of BMD measurements (€ 100/measurement), the yearly intervention cost was €600 the first year and €550 in subsequent years for a persistent patient. To achieve meaningful ICERs, patients in the fully adherent arm were assumed to be on a drug 50% more expensive (€600/year), and that represented a newer "high adherence drug". The yearly intervention cost in the full adherence arm was €800 for the first year and €750 in subsequent years. Sensitivity analyses were conducted where drug costs were assumed to be equal.

Quality of life

The reduction in QoL the year after an osteoporotic fracture was derived from the KOFOR study [30, 34]. The average 1-year QoL loss (area under curve) was divided by the QoL before the event to calculate a measurement of the proportional disutility of a fracture. The first-year disutility multipliers were 0.80, 0.65 and 0.93 for hip, vertebral and wrist fractures respectively. The QoL in subsequent years after a hip fracture was assumed to be 90% of that of a healthy individual [6]. A case-control study of patients enrolled in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial showed that the QoL was reduced by approximately 9% when a clinical vertebral fracture had occurred previously at an unknown time [35]. Based on these findings, we conservatively assumed that the QoL the second and following years for a clinical vertebral fracture was 0.05, which gave a multiplier of 0.93. Wrist fractures were not associated with any utility loss beyond the first year.

Mortality

The age-specific annual mortality rates for the general population in Sweden were based on the years 1998–2002 [26]. Swedish age-specific post-hip and post-clinical verte-

Table 2 Proportion of patients going to long-term care (LTC) after hip fracture

Age at fracture (years)	Proportion to LTC
50	0.067
60	0.065
70	0.102
80	0.147
90	0.226

[32]

bral mortality rates the first and following years after a fracture event were derived from studies by Odén et al. [36] and Johnell et al. [37]. In accordance with previous findings [38, 39], it was assumed that 30% of the excess mortality after a hip or a vertebral fracture was caused by the fracture. The remaining excess mortality was attributed to the higher degree of frailty after a fracture compared with the general population. Wrist fracture was assumed not to be associated with any excess mortality [40].

Model validation

The model output was successfully validated against the International Osteoporosis Foundation (IOF) reference model [41, 42] and estimated cumulative hip fracture rates were validated against the Swedish hip fracture incidence [27] and mortality in the normal population [26]. Small differences in estimated fracture risks were found, as expected, because the adherence model used somewhat different assumptions, for example, it allowed vertebral fractures after hip fractures, used a cycle length of 6 months instead of 1 year, and allowed each patient's individual fracture history to be tracked when post-fracture mortality was calculated. The results from the adherence model were also subject to first-order uncertainty as is inherent in trial simulations.

When persistence was isolated in the model by disregarding effects from FOB and primary non-adherence, patients in the full adherence arm sustained 32% fewer hip fractures than in the partial adherence arm when simulations were run for 3 years. Although not directly comparable, the figure is similar to published estimates [16, 17, 43].

Presentation of the base case

The base case population was defined to be at the threshold of osteoporosis, but still with a relatively low fracture risk (Table 3).

Table 3 Base case characteristics

Characteristic	Statistic
Age (years)	70
Average T-score (SD)	−2.5
Prevalent vertebral fracture	No
Incidence of primary non-adherence (%)	4
Fraction of benefit (%)	80
Annual drug price partial/full adherence alternatives (€)	400/600
Treatment duration (years)	5
Offset time for persistent patients (years)	5
Fracture risk reduction from treatment (%)	50
Persistence	See Persistence

Drivers of cost-effectiveness

Determining what drives cost-effectiveness of a high-adherence alternative is complex, since low adherence often is associated with lower intervention costs (drugs, BMD scans and physician visits), which will favour the low adherence alternative. To determine which variables had the greater impact on cost-effectiveness, the "variable-dependent elasticity" (VDE) was assessed. Elasticity measures the responsiveness of the outcome to changes in the value of an input parameter [44]. In this study, we defined VDE as the percentage change in the ICER that occurred in response to a percentage change in a given variable. For example, if, in response to a 20% increase in the price of the high adherence drug, the ICER increased by 10%, the VDE would be 10/20 = 0.5.

$$\mathrm{VDE} = \frac{\text{Relative \% change in the ICER}}{\text{Relative \% change in variable X}} \quad (1)$$

The VDE was determined for the FOB, drug efficacy, duration of treatment, dropout rate, primary non-adherence, offset time, discount rates, cost of fractures and the pretreatment fracture risk. The estimate allowed a given variable to freely vary ±50% around its base case value, based on uniform distributions (all values were equally likely to be sampled). A total of 1,000 different ICERs were created in the simulation model. For these 1,000 samples, both the ICER and the variable were log-transformed to give a percentage change [44] rather than a change in the magnitude of the non-transformed variable. In the absence of transformation, for example, an increase in the treatment duration by X years would increase the ICER by Y euro (€), which would make the variables difficult to compare. A multivariate linear regression was then performed where the logarithms of each variable were the independent and the logarithm of the ICER the dependent variable (a log–log model). The coefficients should be interpreted as the average VDE over the whole ±50% range around the base case (e.g. an increase in the risk of fractures by 1% will, on average, decrease the ICER by 1.73%).

Changes in variables were, as far as possible, made for both treatment arms simultaneously. FOB, relative risk of dropping out and primary non-adherence could only be altered in the partial adherence arm. For simplicity of interpretation, drug price was only changed in the full adherence arm.

Results

Base case analysis

The base case analysis included a no treatment arm (Table 4). The comparison partial adherence vs no

Table 4 Base case analysis, including a no treatment arm (€)

	No treatment	Partial adherence	Full adherence	Difference	
				Partial vs no treatment	Full vs partial
Treatment cost	0	1,101	3,434	1,101	2,333
Fracture costs	14,626	14,022	12,401	−604	−1,621
Total cost	14,626	15,123	15,835	497	712
Number of hip fractures	0.400	0.390	0.364	−0.009	−0.027
Life years	15.3985	15.4076	15.4289	0.009	0.021
QALYs	7.7588	7.7739	7.8118	0.0151	0.0379
NNT to avoid a hip fracture	–	107	37		
ICER				32,914	18,809

QALYs = quality adjusted life years; NNT = number needed to treat; ICER = incremental cost-effectiveness ratio

treatment represents how a typical anti-fracture drug (e.g. a bisphosphonate) compares with no treatment if adherence in clinical practice is taken into account. Both incremental costs and effects were, as expected, quite low when the effects of poor adherence were included.

In the partial adherence arm, the higher drop-out rate and the assumed reduction in FOB markedly reduced the QALYs gained and increased the total treatment cost. Compared with the partial adherence arm, 0.038 QALYs were gained and considerably fewer patients (37 vs 107) needed to be treated to avoid a hip fracture in the full adherence arm, showing the added value of improved adherence. It should be noted that this benefit came at a considerably higher treatment cost, which to some extent was offset by saved fracture costs. The results in Table 4 also show that considerably fewer QALYs are gained with oral medication when poor adherence is taken into account.

Age, risk groups and FOB

Table 5 shows the cost-effectiveness analysis for women aged 60–80 years, with or without prevalent vertebral fractures and with or without 100% FOB. The table shows that the cost-effectiveness of the full adherence alternative was improved in high-risk patients (i.e. those with a prior vertebral fracture), mainly due to a higher number of fractures avoided, whereas drug costs were largely unaffected by changes in the fracture risk. In other words, treating patients with a higher fracture risk will increase the number of avoided fractures without increasing the treatment costs. Treating patients with improved persistence will also avoid more fractures, but will also generate increased drug costs. As expected, if full FOB was assumed in the partial adherence arm, the full adherence alternative became less cost-effective.

Cost-effectiveness was also assessed at varying baseline T-scores. As seen in Fig. 4, the cost-effectiveness improved markedly with every half point decrease in the baseline T-score value. This is because the risk of fracture increases with decreasing T-score, and so does the potential benefit of full adherence.

Analysis of persistence

A separate analysis was performed on the incidence of non-persistence (Table 6). This was done by varying the relative risk (RR) of not persisting with treatment. An RR of 0.8 would thus reduce the drop-out rate by 20% in each cycle compared with the base case.

A high drop-out rate (low persistence) in the partial adherence arm adversely affected cost-effectiveness, which in turn beneficially affected the incremental cost-effectiveness of full adherence. The effect on the ICER was relatively small since decreased persistence was associated with lower treatment costs. When drug costs were assumed to be the same for the two treatment alternatives, the full adherence arm was cost saving due to more avoided fractures. Notwithstanding equal drug prices, the incremental treatment cost of full adherence continuously increased with higher drop-out rates, since more doses were then taken.

Table 5 The ICER (€) for women aged 60–80 years with or without prevalent vertebral fractures (VF) and with or without 100% fraction of benefit (FOB)

Full adherence vs partial adherence	Age (years)		
	60	70	80
T-score −2.5, no prevalent VF, FOB 80%	52,301	18,809[a]	Cost saving
T-score −2.5, prevalent VF, FOB 80%	14,384	Cost saving	Cost saving
T-score −2.5, no prevalent VF, FOB 100%	60,073	25,177	Cost saving
T-score –2.5, prevalent VF, FOB 100%	19,089	Cost saving	Cost saving

[a] Base case

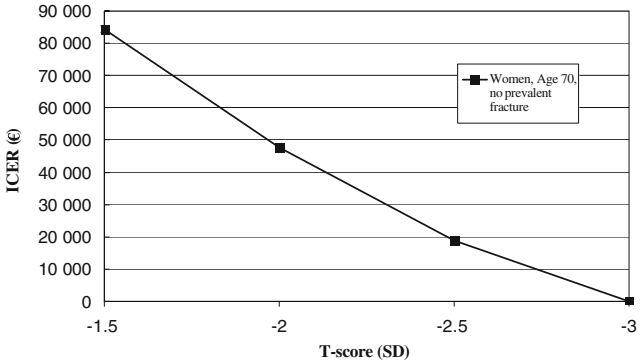

Fig. 4 Cost-effectiveness as a function of T-score (SD), full adherence vs partial adherence in women aged 70 years

Switching

Two estimates of switching medication were assessed (Table 7). Introducing switching was associated with more QALYs in the partial adherence arm, but was also associated with extra costs, resulting from an extra visit to a physician and the continued cost of treatment with a drug. Thus, the effect of a larger proportion of the *partial adherence* cohort still being on medication was to a large extent offset by the extra costs.

Offset of treatment effect after discontinuation and onset of drug effect

In the base case, the offset time was assumed to be equivalent to the time on treatment. Two additional offset scenarios were examined: one where the offset time was 5 years irrespective of the time of drop-out and the other where an offset time of zero was assumed. Assumptions regarding offset time had a large impact on cost-effectiveness (Table 8). In contrast to the base case, both treatment alternatives shared the same offset properties in the sensitivity analyses, and this explains the higher ICERs. When treated patients had an offset time of zero, loss of effect due to poor persistence was always accompanied by decreasing treatment costs, since there was no "free" drug effect in either of the two arms. The better ICER in the scenario where a 5-year offset time was assumed for all patients was because the risk of fracture increased with age, and patients reached higher ages with a persisting drug effect in this scenario. The older the patient, the higher the fracture risk will be during the period when the "free" drug effect is decreasing fracture risk. This decreased the number of fractures in the full adherence arm to a greater degree and thus improved the cost-effectiveness compared with the scenario with an offset time of zero.

Onset time did not have a large impact on cost-effectiveness since both partially and fully adherent patients sustained more fractures when an onset time was assumed. As shown in Table 8, cost-effectiveness actually worsened compared with the base case since a larger proportion of patients in the full adherence arm received treatment during this period of onset when the drug effect was incomplete.

Important variables affecting cost-effectiveness

As indicated in the Materials and methods section, when a change in an input variable of a given proportion results in a comparable change in the ICER, the variable dependent elasticity (VDE) equals 1.0. The larger the VDE, the larger the impact of the input variable on the cost-effectiveness. Positive values indicate that the ICER increased when the input variable value was increased, whilst negative values indicate that the ICER decreased (Table 9). For example, an increase in the risk of fracture by 20% lowered the ICER by 40% (−2.0*20%).

Our results show that the VDE values ranged from 0 to 2.7. Changes in FOB (VDE=1.1), drug effect (VDE=−2.2), offset time (VDE=−0.7) and risk of fractures (VDE=−2.0) had a large impact and affected both costs and QALYs

Table 6 Effect of changing the drop-out incidence when comparing full adherence with partial adherence (€/QALY)

Persistence analysis				
RR of dropping out of treatment compared with base case	0.5	0.8	1.0[a]	1.2
QALYs gained in the full adherence arm compared with the partial adherence arm	0.0278	0.0343	0.0379	0.0402
Proportion of the initial cohort that dropped out during the treatment period	0.45	0.62	0.71	0.77
Analysis with base case assumption 1.5 × drug price (€ 600/€ 400)				
Saved fracture cost (full adherence)	−1,128	−1,473	−1,621	−1,755
Extra treatment cost (full adherence)	1,806	2,144	2,333	2,493
ICER	24,367	19,548	18,809	18,360
Analysis with equal drug price for the treatment alternatives				
Saved fracture cost (full adherence)	−1,128	−1,473	−1,621	−1,755
Extra treatment cost (full adherence)	904	1,242	1,431	1,591
ICER	Cost saving	Cost saving	Cost saving	Cost saving

[a] Base case persistence

Table 7 The effect of switching treatments on cost-effectiveness (€/QALY gained)

	Proportion switching (%)	ICER
Base case	0	18,809
Melton et al. [52]	19	19,144
McCombs et al. [53]	31	19,907

simultaneously to jointly "push" the ICER in a single direction. For example, when the risk of fractures was increased, more fractures were avoided, which also saved fracture-related costs. The same pattern applied with an increased effect of the drug, since the benefit of full persistence in the full adherence arm resulted in a larger increase in the number of avoided fractures than in the partial adherence arm.

Conversely, when the risk of dropping out of treatment (VDE=−0.2), intervention duration (VDE=0.5), or primary non-adherence was changed (VDE=0), the impact on cost-effectiveness was dampened because costs and effects partially offset each other. For example, a higher persistence generated more QALYs, but also incurred higher treatment costs. Primary non-adherence had, in our model, no effect on the ICER, since changes in effects were totally offset by changes in cost.

As expected, drug price (VDE=2.7) and cost of fractures (VDE=−1.2) influenced the cost-effectiveness ratio. Although the cost of fractures was much higher than the treatment cost, the variable had less impact because it only made a difference for patients who sustained a fracture whilst the change in drug price affected the entire treated population.

Discussion

Health economic modelling of anti-fracture therapies is a thoroughly researched area, and many publications are available on the topic. However, adherence is seldom included in the cost-effectiveness models. Poor adherence is commonly believed to have an impact on cost-effectiveness in clinical practice, since poor adherence reduces costs as well as outcomes. Of greater relevance is that with poor adherence many fewer patients will be properly treated, and thus fewer fractures prevented, which is the principal goal of treatment. Nevertheless, cost-effectiveness analysis is also important since future improvements in fracture prevention may come not only from more effective treatments, but also through improved drug delivery and adherence. Thus, the prices, costs and cost-effectiveness of these new alternatives need to be compared with the present alternatives in clinical practice.

Table 8 Offset and onset of drug effect (€/QALY)

	ICER
Base case	18,809
Always 5-year offset time	35,523
No offset time assumed	54,803
1-year onset time	20,833

Table 9 Variable dependent elasticity (full vs partial adherence)

Variable	Average VDE
Fraction of benefit[a]	1.1
Drug effect	−2.2
Intervention duration	0.5
Risk of dropping out of treatment[a]	−0.2
Drug price[b]	2.7
Primary non-adherence[a]	0.0
Offset time	−0.7
Discount rates (both costs and effects)	0.4
Cost of fractures (including long-term care)	−1.2
Risk of fractures	−2.0

[a] Variable only changed in the partial adherence arm
[b] Drug price was only changed in the full adherence arm

This article introduces a theoretical modelling framework for this increasingly important area of osteoporosis modelling and identifies several important drivers of cost-effectiveness. Our model compared conventional drug treatment, associated with suboptimal adherence, with a hypothetical fully adherent population. It should be noted that such a population probably does not exist, and that even a drug regimen with 6-monthly or yearly dosing intervals would be subject to patient drop-outs. In previous economic studies of persistence [45, 46], including one commissioned by the National Institute for Health and Clinical Excellence (NICE) [46], it was assumed that 20–80% of patients completed the full 5-year course, with the remaining patients receiving 3 months of drug costs, but no health gain. A problem with this approach is that those who discontinue treatment are likely to do so at time points throughout the 5-year period and should thus receive some health benefit as well as additional drug costs. How this approach changes the cost-effectiveness compared with the approach in the present analysis is unclear, but if osteoporosis models that incorporate adherence should evolve beyond the crude methods previously employed, there are several gaps in empirical data that need to be filled. Information is lacking, for example, on the relation between treatment duration and offset time, the reduction in FOB from poor compliance, and country-specific persistence and compliance data. In our study, the components of adherence were separated into compliance and persistence in order to assess their impact on cost-effectiveness. The

often-used measure of MPR was not considered because it sometimes blurs the distinction between persistence and compliance, which should not necessarily be linked to each other. However, this does not preclude the present modelling framework from being used with fracture risks elicited from studies using MPR estimates from retrospective data. Although problematic, they are the best data presently available for describing the link between fracture rates and adherence. The inclusion of compliance and FOB in the evaluation of treatments that have high persistence rates should be explored thoroughly. In some instances, the benefit of improved compliance may already be captured by RCTs. For example, the marked 77% reduction in clinical vertebral fractures with zoledronic acid [47] may be partially due to better drug compliance. For this reason, a conservative approach to modelling compliance in health economic evaluations is appropriate, until more evidence becomes available.

The drivers of cost-effectiveness were explored by randomly changing variables, and then, in a log–log regression model, by assessing their individual effect on the ICER comparing full adherence with partial adherence. The variables that on average had the greatest effect on the ICER included the efficacy of the intervention, drug price, risk of fractures, FOB, and fracture-related costs. For example, a 1% increase in general drug effect lowered the ICER by 2.2%, and a 1% increase in the drug price of the high-adherence comparator increased the ICER by 2.7%. When comparing the VDE of these variables with each other, one should keep in mind that they will differ in how likely they are to undergo large changes.

The benefits of increased persistence are, to some extent, neutralised by the fact that much of the gain on the effect side is offset by cost savings due to lower drug costs in the partial adherence arm. Although many of the benefits of high adherence are to some extent offset by higher drug costs, the ICER did decrease when the difference in persistence was increased, indicating that high persistence can improve cost-effectiveness as long as the difference in drug price is not too large. The cost offset will also be dependent on what fracture costs and other intervention costs are used in a model. It was clear that the cost-effectiveness of high adherence is better in high risk populations since more fractures will be avoided. However, this is not surprising and the pattern is similar for most diseases and treatments.

The assumption that the lingering anti-fracture effect is longer if the patient has taken the drug longer is important since it implies anti-fracture effect without drug costs. When offset time was assumed to be equal in both arms, incremental cost-effectiveness of full adherence worsened markedly. The same applies to FOB since it represents an effect reduction without cost savings. If FOB is based on MPR, a drug cost reduction might be necessary and a cost offset would also affect cost-effectiveness in this case. Other aspects such as switching, primary non-adherence and onset time were found to be of lesser importance due to cost offsets and scenarios where both partially and fully adherent patients are affected similarly.

This study had some limitations. First, the base case results are critically dependent on assumptions regarding both costs and effects. Second, although we undertook sensitivity analyses, these will be affected by the base case that we used. This is also true for the analysis of VDE, which is affected by the chosen base case. For example, changing a variable can have a different impact on the ICER depending on the starting assumption for that variable (i.e. the ICER and particular variable will not always have a linear relationship, and the VDE can therefore be over- or underestimated at different points along the ±50% range of the variable values). This non-linearity can make the exercise seem arbitrary, but the average VDE will still be an indicator of which variables are governing the ICER. The persistence data used in this analysis were taken from a large claims database from the US. It is likely that drug persistence is dependent on a number of factors, such as drug costs, insurance status [48] and cultural setting, and can thus vary between countries and even within countries. As persistence levels potentially vary between settings, so will the cost-effectiveness of improving it. Compliance with treatment recommendations and consistency of refilling are also likely to differ between health-care systems and cultural settings. For example, Lillard et al. [49] showed that insurance coverage for prescription drugs increases the probability of use. Thus, when evaluating the cost-effectiveness of drugs that improve persistence and/or compliance it is important that country-specific data are used where possible, not only for fracture risks and costs, but also for adherence. In this study, US persistence data were combined with Swedish cost and epidemiological data, but since no attempt was made to evaluate the cost-effectiveness of a particular therapy, this is of minor importance.

Conclusions

In this article we describe a modelling framework that incorporates adherence in health economic modelling of osteoporosis. Adherence is one of the most complex aspects of health economics, and future evaluations will need to be carefully constructed to maintain external validity. From a health economic perspective, high adherence is particularly important when treating high-risk populations. Cost-effectiveness of treatments that confer high adherence will be sensitive to assumptions regarding

offset time and drug effect reductions from poor compliance. The health benefits of improved adherence are often partially offset by increased intervention costs that are associated with the improved drug-taking behaviour. Nonetheless, our results indicate that high adherence is likely to be associated with added value for the health-care system.

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