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REVIEW

Non-compliance: the Achilles' heel of anti-fracture efficacy

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Abstract About 50% of patients fail to comply or persist with anti-osteoporosis treatment regimens within 1 year. Poor compliance is associated with higher fracture rates. Causes of poor compliance are unknown. As it is not possible to predict poor compliance, close monitoring of compliance is needed. Despite evidence supporting the anti-fracture efficacy of several pharmacological agents, approximately 50% of patients do not follow their prescribed treatment regimen and/or discontinue treatment within 1 year. Poor compliance is associated with higher fracture rates and increased morbidity, mortality and cost. However, as poor compliance, even to placebo, is associated with adverse outcomes, the higher morbidity appears to be only partly the result of lack of treatment: as yet, undefined characteristics place poor compliers at higher risk of morbidity and mortality. Only a small proportion (e.g., 6%) of the variability in compliance is explained by putative causal factors such as older age, co-morbidity or greater number of medications. Regimens with longer dosing intervals, such as weekly dosing, improve compliance, persistence and outcomes, but only modestly. As it is not possible to predict poor compliance, close monitoring of compliance should be an obligatory duty in clinical care. How this is best achieved has yet to be established, but poor persistence occurs as early as 3 months of starting treatment, indicating the need for early monitoring.

Keywords Compliance · Osteoporosis · Persistance

Introduction

Increased longevity has resulted in the emergence of age-related fragility fractures as a major public health

problem, with a lifetime risk of vertebral, hip and other peripheral fractures of 46% for women and 22% for men [1]. These fractures are associated with an increase in morbidity and mortality that imposes a huge healthcare burden on the community [2–4], with an estimated annual cost of €30 billion in Europe and $17 billion in the USA [5, 6]. The recognition of this problem has resulted in the development of a range of therapeutic agents shown to produce an early and sustained reduction in fracture risk [7]. In addition, methods of identifying high-risk individuals allow cost-effective targeting of treatment to those most likely to benefit, avoiding needless exposure to treatment of those at low risk of sustaining a fracture [8–12].

Despite this progress, two impediments threaten efforts to reduce the public health burden of fractures. First, most individuals with fragility fractures remain undiagnosed and untreated [13–15], and second, among individuals identified as being at risk of fracture, over 50% are either poorly compliant or poorly persistent with treatment within 12 months. Poor compliance is the failure to take the prescribed treatment regimen (dose and frequency) and poor persistence is the failure to continue treatment for the length of time prescribed (Box 1) [16, 17].

Box 1. Definitions of medication compliance and persistence [16, 17].

Medication compliance (synonym: adherence): "The extent to which a patient acts in accordance with the prescribed interval and dose of and dosing regime."

Medication persistence: "The accumulation of time from initiation to discontinuation of therapy, measured by a time metric."

Here, as a first step towards its solution, we attempt to increase awareness of the problem of poor compliance and persistence in osteoporosis. We define the size of the problem and the challenges associated with identifying the causes, medical consequences and health costs of poor adherence to therapy, and discuss its pragmatic management in clinical practice.

The size of the problem of poor compliance and persistence in clinical practice

Peer-reviewed literature in osteoporosis from 1985 to 2006 was examined using MEDLINE®, EMBASE® and BIOSIS and predefined search criteria (Box 2) to identify clinical studies concerning the prevalence, putative causes and effects of poor compliance and persistence in clinical practice, and strategies that address these problems. We retrieved 44 relevant clinical studies, six of which had adequate data to address the issues we posed.

Box 2. Literature review: Compliance and persistence in Osteoporosis.

Data sources and search strategy

Sources of data identified by systematically searching the electronic databases MEDLINE®, EMBASE® and BIOSIS for papers on compliance/persistence in osteoporosis published from 1985 to 2006. Only clinical studies in the English language were retrieved.

Search terms: osteoporosis, compliance, persistence, adherence

Study selection

Patients

The patient population of interest was adult (aged ≥18 years) women and men of any race receiving drug treatment for the management of osteoporosis.

Studies in individuals with normal bone mineral density or that included a paediatric/adolescent population were excluded.

Types of studies

Randomised clinical trials (RCTs; any design) or meta-analyses of RCTs. Observational studies, case-control studies, cohort studies, cross-sectional studies, and Phase I and II trials.

Individual case reports and review articles were excluded.

Intervention

Articles in which patients received pharmacological therapy for the management of osteoporosis (prevention/treatment).

Studies in which these drugs were given for any condition other than for the management of osteoporosis (eg, menopausal symptoms or optimisation of peak bone mass) were excluded. Studies of investigational drugs for osteoporosis, dietary calcium/vitamin D, lifestyle measures, hip protectors, other devices and other non-pharmacological approaches (eg, mechanical stimuli) were excluded.

Outcome measures of interest

Only studies reporting patient compliance and/or persistence rates (and defining these) with prescribed osteoporotic medication were included.

Studies that did not differentiate between patients treated for osteoporosis and other subgroups (eg, in a HRT study) were excluded.

The reports were based on administrative databases that record prescriptions (European Union) or paid prescription claims (USA). These approaches document prescription filling, not drug consumption, used to average the refills over long periods of time to estimate treatment compliance and persistence with the prescribed regimen (e.g., daily, weekly). They provide few details of characteristics of patients, fracture risk or bone mineral density (BMD). The records do not define the indication for treatment, so medication such as hormone replacement therapy may have been prescribed for reasons other than fracture prevention. Also, information is not available concerning the reason for stopping treatment, so non-persistence may be appropriate in some circumstances (e.g., adverse events).

Persistence is usually calculated as the duration of time from initiation of treatment (or start of follow-up) to the final refill (or end of follow-up); for example, 180 days from first to last refill. The period covered by the last

prescription, which may be up to 3 months, is often included. However, persistence may be underestimated using this definition if patients switch to alternative bone-protective treatments. Compliance is often defined as the medication possession ratio (MPR), which is calculated as the number of tablets dispensed divided by the number of days between refills; for example, 300 tablets/365 days= 82% compliance. It should be noted that this definition does not provides information about how consistently prescriptions were refilled, whether the drug was taken according to instructions or even whether it was taken at all.

The review revealed that more than half of patients fail to comply and/or persist with the prescribed regimen during the first year of treatment (Table 1) [18–26]. An example of medication persistence in one of these studies in patients receiving bisphosphonates is shown in Fig. 1 [23]. Irrespective of whether the bisphosphonate dosing was daily or once-weekly, there was a rapid drop-off in prescription refills (non-persistence) during the first 3 months of therapy, with continued decline during the following 9 months. Compliance rates representing the number of doses taken during the periods when refills were obtained ranged between 43–81% (Table 1); compliance was better for weekly than daily dosing but only modestly so (Table 1).

The morbidity and mortality associated with poor compliance and persistence

Four studies have addressed the association between poor compliance with bisphosphonates and subsequent fracture risk (Table 2) [18–20, 26]. The first analysed a health service database from Saskatchewan, Canada, where over

Table 1 Summary of studies using administrative databases to describe the extent of compliance/persistence in osteoporosis

Reference	Details of database/ patients	Follow-up (mean, y [if stated])	Drugs prescribed	Mean compliance[a]	% with ≤80% compliance during follow-up	% persisting at 1 yr unless otherwise stated[b]
[24]	CANDOO database 1967 f & m (mean age 65.8 y)	1990–2001	Etidronate (61%), alendronate (24%), HRT (15%)	Not stated	Not stated	85.7%
[19]	Saskatchewan 11,249 f (mean age 68.4 y)	1/96–3/01 (2.0)	Etidronate/calcium (60.9%), HRT (27.8%), alendronate (10.8%), other (0.5%)	70.0%	50.6%	2 y: 60.0%
[18]	US health insurer 58,109 (93.6% f; mean age 58.7 y)	1/98–8/01 (1.0)	HRT (91.0%), BP (6.4%), raloxifene (2.6%)	1 HRT: 73% 2 HRT: 81% BP: 68% Raloxifene: 61%	Not stated	1 HRT: 23.5% 2 HRT: 30.7% BP: 24.2% Raloxifene: 17.9%
[23]	US health claims database 2741 f[c]	1/97–7/02 (1.0)	BP, daily (74%), weekly (26%)	Daily: 57.6% Weekly: 69.2%	Daily: 59.6% Weekly: 44.7%	Daily: 31.7% Weekly: 44.2%
[20]	US managed care 38,120 f (mean age 66 y)	1/97–6/02 (1.7)	Alendronate (33.2%), risedronate (2.1%), HRT (64.7%)	1 y: 65.5%	74.0%	78.0%
[22]	NDC Health database 211,319 f (age >50 y)	10/02–9/03 (1.0)	BP, daily (16%), weekly (84%)	Daily: 54.0% Weekly: 65.0%	Daily: 65.0% Weekly: 55.0%	Not stated
[21]	US Medicare/PACE 40,002 f & m (mean 60 y)	1/96–12/02	BP (46.9%), calcitonin (29.4%), HRT (13.2%), other (10.5%)	Not stated	Not stated	54.8%[d]
[26]	US managed care 35,537 f (mean 65 y)	9/99–12/01	Alendronate (84.9%), risedronate (15.1%)	Not stated	2 y: 56.8%	2 y: 20%
[25]	US managed care 13,455 f (mean age 68.8 y)	1/02–12/03	Weekly alendronate	Not stated	Not stated	50.4%[e]

BP, bisphosphonates; CANDOO, Canadian Database of Osteoporosis and Osteopenia; f, females; HRT, hormone replacement therapy;m, males; NDC, National Drug Code; PACE, Program for All-Inclusive Care for the Elderly; y, years[a] Number of days of tablets supplied (from first to last prescription) within the first 12-month follow-up, divided by the 365-day follow-up, unless otherwise stated; [b] Number of days from the first dispensing of bisphosphonate to the end of the last dispensing, unless otherwise stated; [c] Patients who switched between daily and weekly BP were excluded; [d] Defined as 120 days without refilling prescription; [e] Based on a 60-day refill gap

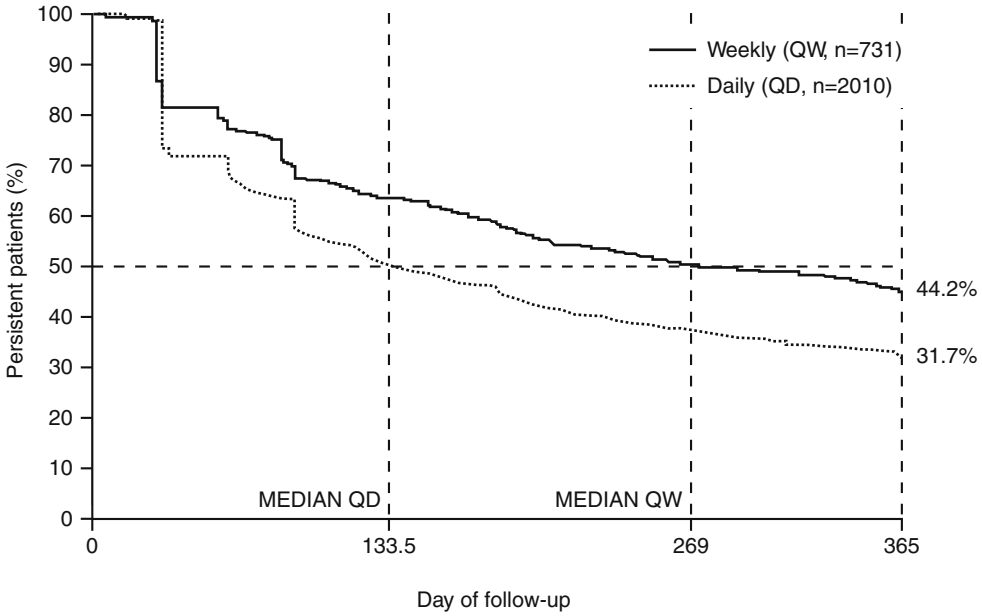

Fig. 1 Persistence with daily and weekly bisphosphonate (alendronate, risedronate) therapy among 2741 women with postmenopausal osteoporosis during their first year of therapy [23]. Data were obtained from a US managed care database. Figure reprinted from Curr Med Res Opin, 21, Cramer JA, Amonkar MM, Hebborn A, et al, Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis, 1453-60, Copyright (2005), with permission of Librapharm

99% of residents are covered by a health insurance plan and all prescriptions are recorded electronically [19]. High compliance with bisphosphonates (defined as MPR >80%) during 2 years of follow-up was associated with 18.7% fewer fractures than poor compliance (MPR <80%) ($p< 0.005$). Increases in fracture risk of up to 40% were observed in those patients with ≤50% compliance, while minimisation of fracture risk required >90% compliance. A second study involved 38,120 patients from a US managed care population covered by private and public benefit plans [20]; the follow-up period of this study captures the introduction of weekly bisphosphonates. Poor compliance (defined as MPR ≤50%) was associated with a 16.7% higher fracture risk during a mean of 1.7 years' follow-up. Compared with ≥90% compliance, fracture risk was higher as compliance diminished: 9.1% for 80–90% compliance, 18.3% for 50–80% compliance and 21.0% for <50% compliance (Fig. 2). Poor compliance was also associated with a 37% increase in the risk of all-cause hospitalisation and mean average healthcare monthly costs were almost

Table 2 Effect of compliance/persistence on fracture rates

Reference	Details of database/ patients	Follow-up(mean, y [if stated])	Drugs prescribed	Compliance[a]	Fracture rate during follow-up	Effect of good compliance on fracture risk
[19]	Saskatchewan 11,249 f (mean age 68.4 y)	1/96–3/01 (2.0)	Etidronate/calcium (60.9%), HRT (27.8%), alendronate (10.8%), other (0.5%)	70.0%	9.7%[b]	↓18.7% when compliance ≥80% vs compliance <80%
[20]	US managed care 38,120 f (mean age 66 y)	1/97–6/02 (1.7)	Alendronate (33.2%), risedronate (2.1%), HRT (64.7%)	1 y: 65.5%	10.2%[b]	↓16.7% when compliance ≥80% vs compliance <80%
[26]	US managed care 35,537 f	(2.0)	Alendronate (84.9%), risedronate (15.1%),	2 y: 43.2%	8.0%	↓21% when compliance ≥80% vs <80%
[18]	US health insurer 58,109 (93.6% f; mean age 58.7 y)	1/98–8/01 (1.0)	HRT (91.0%), BP (6.4%), raloxifene (2.6%)	1 HRT: 73% 2 HRT: 81% BP: 68% Raloxifene: 61%	1.43%[c]	↓62% hip fracture and ↓40% vertebral fracture in patients with 1 y of uninterrupted therapy

BP, bisphosphonates; f, females; HRT, hormone replacement therapy; m, males; y, years[a] Number of days of tablets supplied (from first to last prescription) within the 12-month follow-up period, divided by the 365-day follow-up, unless otherwise stated; [b] Any first fracture excluding fractures occurring within 180 days of index prescription; [c] Includes fractures of the vertebrae, lower arm, wrist and femoral neck only

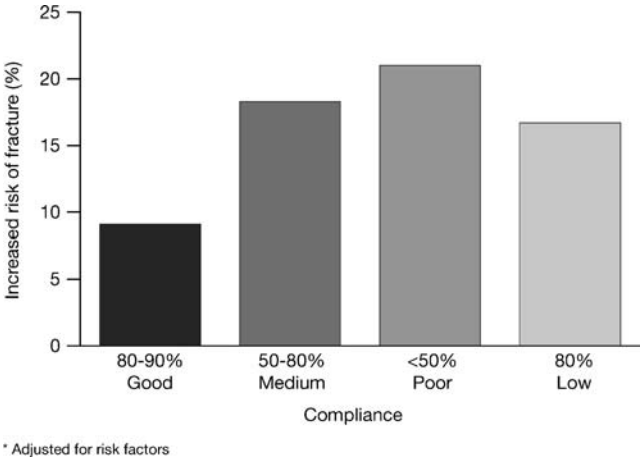

Fig. 2 Relationship between compliance and fracture risk in a cohort of 38,120 women with postmenopausal osteoporosis [20]. Data were obtained from a US managed care database

double: $600 versus $340 ($p<0.0001$) for those patients with good compliance (defined as MPR >90%).

In the third study, also from the USA, Siris et al. [26] report that among 35,537 women prescribed a bisphosphonate, 43.2% (n=15,348) were compliant over the 24-month study (≥80% MPR [27]). Compliant women had a 21% lower fracture risk overall (20% for non−vertebral and 37% for hip) than non-compliant women. Figure 3 shows that in women receiving bisphosphonates, the probability of sustaining a fracture started to decrease above compliance levels of around 50–60% and continued to decline with improving compliance up to 90–100%. Four-fifths of this patient population were also not persistent (>30 days between prescription refills) over the 24-month follow-up period. In the 20% of patients who did persist with medication (≤30 days between refills), the fracture rate was 29% lower overall than in patients who did not persist (40% for vertebral, 29% for non−vertebral, 45% for hip [all $p<0.0001$] and 23% for wrist fractures [$p<0.02$]). In the final study, involving more than 58,000 women from the USA, poor compliance was associated with an increased risk of hip and vertebral fractures and higher healthcare costs (Table 2) [18]. Poor compliance has also been associated with smaller increments in BMD [28].

Difficulties in attributing causation: poor compliance with placebo and adverse outcomes

The observational studies described above support a causal relationship between poor compliance and persistence and morbidity in osteoporosis. However, factors other than insufficient medication, such as demographic and lifestyle factors, co-morbidities and concurrent medications, may have contributed to the higher fracture incidence in poorly compliant or persistent patients. Several lines of evidence support this view. The most important are observations from other disease areas in placebo-treated individuals. For reasons that are not understood, poor compliance even with placebo appears to be associated with an increase in adverse outcomes. In the Coronary Drug Project, good compliance with clofibrate was associated with lower 5-year mortality than poor compliance (15% versus 25%) [29]. However, good compliance with placebo was associated with lower 5-year mortality than poor compliance with placebo (15% versus 28%). This observation was replicated in a study of secondary prevention of coronary heart disease [30]. At

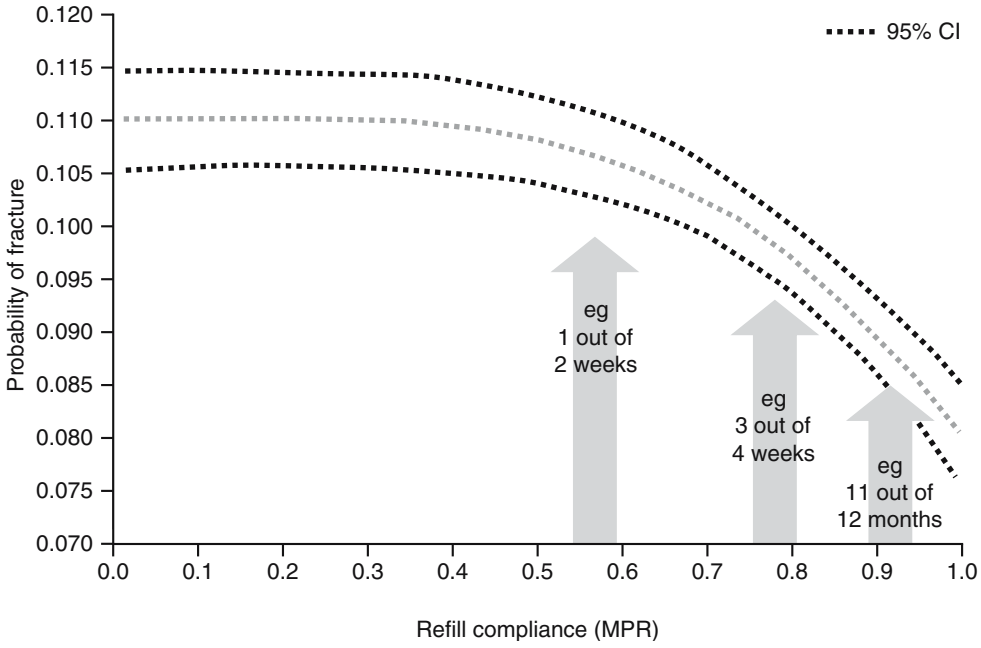

Fig. 3 Relationship between probability of fracture at 24 months and compliance in a cohort of 35,537 bisphosphonate_treated women [26]. Data were obtained from a US managed care database. Reproduced with permission, Professor E. Siris, Colombia University, New York City, NY, USA [**journal permission to be obtained after publication**]

1 year, mortality risk among poor compliers relative to good compliers with propranolol was increased 3.1-fold, while the mortality risk among poor compliers relative to good compliers to placebo was increased 2.5-fold.

Poor compliers to an intervention may have co-existing risk factors that partly explain the higher morbidity and mortality. In the study of clofibrate, poor compliers in the placebo group did have a higher prevalence of risk factors but mortality adjusted for these confounders did not change (16% versus 26%), so an explanation for the higher mortality was not available [29]. Likewise, in the propranolol study, a multivariate analysis did not support the notion that independent factors increasing the risk of heart disease accounted for the findings [30]. The interpretation of these data is difficult but it is probable that poor compliers fail to follow recommendations for other health behaviours; for example, with respect to diet and exercise. These issues are reported in the literature on the health belief model [31]. Conversely, good compliers tend to have better outcomes even if that medication is a placebo.

Calcium and fracture rates in the Women's Health Initiative study

Compliance with treatment may also affect the interpretation of clinical trials, as found in the Women's Health Initiative (WHI) study. The WHI enrolled 36,282 postmenopausal women aged 50–79 years, who were randomly assigned to 1000 mg calcium carbonate with 400 IU vitamin D3 daily or placebo for approximately 7 years [32]. The intention-to-treat analysis showed no evidence of a reduction in fracture risk with the active intervention, with a hazard ratio of 0.88 (95% confidence interval [CI] 0.72, 1.08), for hip fracture, 0.90 (95% CI 0.74, 1.10) for clinical spine fracture and 0.96 (95% CI 0.91, 1.02) for total fracture. The authors, and an accompanying editorial [33], suggested that supplementation with calcium and vitamin D does not reduce the risk of hip fracture. Nonetheless, a post hoc analysis showed that those complying with treatment had a 29% reduction in the risk of hip fractures, leading to the inference that good compliance with the calcium and vitamin D supplementation was associated with a reduction in fracture risk.

The difficulty in interpretation is that the compliers constituted only 60% of the initial cohort randomly allocated to intervention or placebo. The random allotment ensures that known *and* unknown covariates influencing fracture risk independent of treatment are equally prevalent in both groups. However, if the randomisation is violated, an uneven distribution of influential covariates, not the calcium supplement, may be responsible for the lower fracture rate in the treated group in a post hoc analysis.

Causes of poor compliance and persistence in osteoporosis

Examples of putative causes of poor compliance include fear of side effects/safety concerns (particularly following reports in the media), lack of belief that therapy is needed and cost [34]. Much of the data on predictors of poor compliance with osteoporosis therapies are conflicting and no patient or disease characteristics reliably predict compliance or persistence. For example, with respect to age, *both* younger (<65 years) and older age have been reported as being predictive of better compliance/persistence [18, 21, 23, 24, 35–44]. Findings with respect to the influence of previous fractures on compliance are equivocal [36]; educational levels have consistently been reported as having no impact on compliance [45].

None of these putative predictors can be tested using Koch's postulates, so the associations with poor compliance are difficult to verify experimentally. Moreover, in one study using the claims data from over 40,000 patients, potential predictors for poor compliance such as advanced age, co-morbidity, greater numbers of therapies and institutionalisation accounted for only 6% of the variance in compliance [46]. Under the assumption that these factors were truly responsible for the poor compliance, their correction is, therefore, unlikely to substantially modify the burden of poor compliance.

Improving compliance and persistence

Strategies to improve compliance in osteoporosis are emerging but have yet to be evaluated as extensively as in some other chronic diseases. More frequent dosing with bisphosphonates may be associated with poorer compliance, with two large database studies reporting that simplification of dosing regimens of bisphosphonates enhances compliance and/or persistence (Table 1) [22, 23]. However, the small differences between the daily and weekly dosing regimens suggest that women accommodate their lifestyles to their preferred regimen, be this daily or weekly treatment. Women who used both weekly and a new monthly regimen in a crossover trial did express a preference for less frequent dosing on the grounds of convenience [47]. Whether this preference translates into improved compliance/persistence has yet to be determined.

Cooper et al. report that at 6 months both monthly ibandronate and weekly alendronate are associated with poor persistence (defined using a refill gap of ≤14 days, a more stringent definition for this type of analysis than the usual 30 days, therefore potentially underestimated persistence) [48]. In this study, the proportion of patients

persisting with treatment at 6 months was 56.6% with monthly ibandronate versus 38.6% with weekly alendronate [48]. However, the higher persistence with ibandronate could have been the result of a patient support programme with a monthly telephone reminder provided to the ibandronate group only. In the absence of a group receiving ibandronate alone and/or alendronate plus a telephone reminder, it is not possible to determine whether the difference in persistence was the result of less frequent dosing or the patient support programme.

In a randomised study of 75 women with osteopenia treated with raloxifene, monitoring by a nurse improved compliance and persistence by 57% and 25%, respectively [49]. Measurement and feedback concerning levels of urinary-N-telopeptide, a bone remodelling marker, did not further improve either parameter. The IMPACT study showed that reinforcement of osteoporosis treatment using bone turnover marker data in women treated with daily bisphosphonates therapy was associated with fewer fractures (1.2% versus 2.7% p=0.049), which the authors stated could partially be explained by the significant increase in persistence in the reinforcement group when the markers were reduced, producing a positive feedback [50].

The use of an educational leaflet was assessed in a prospective study in 745 postmenopausal women prescribed raloxifene in 126 primary care practices in Spain [51]. At 3 months, compliance, as assessed by the Morisky test, was high in 56.3% of the group provided with the leaflet and 62.7% of the control group; corresponding figures at 12 months were 47.4% and 52.5%, respectively. These self-reported figures suggest that an educational leaflet does not improve compliance. However, Cuddihy et al. assessed the benefits of educational materials in patients with distal forearm fracture [52]. Provision of materials improved the rate of successful intervention compared with the general population (45% versus 16%). Compliance and persistence were particularly high in some subgroups; for example, 100% in women with borderline/normal T-scores (>−1.5). However, it is not clear from the report if this latter group had previously received treatment for osteopenia/osteoporosis.

Economic considerations in improving compliance and persistence

Improving compliance and persistence involves costs as well as benefits. The savings produced by the fractures prevented are offset by the costs of the intervention. Thus, strategies for improving compliance and persistence must be assessed in terms of their cost−effectiveness. Since there are insufficient data from clinical trials to estimate the impact of compliance and persistence on cost-effectiveness, simulations based on data derived from the Swedish population are used [53–58]. In the base case, treating a 70-year-old woman without a previous fracture for 5 years with a drug that halves fracture risk with 100% compliance and persistence costs €544 (5000 Swedish Kronor [SEK]) per year. The cost per quality-adjusted life-year (QALY) gained is €17,445 (Table 3). Assuming that lack of compliance and/or persistence produces a treatment outcome of 80%, 50% and 30% of the fracture risk reduction demonstrated in clinical trials, the cost per QALY increases to approximately €25,000, €48,000 and €89,000, respectively (Table 3). In the last case, the cost per QALY is higher than the Swedish cost-effectiveness threshold (600,000 SEK=€65,303). Table 3 also shows the maximal price for a new intervention with the same efficacy (50% fracture reduction) if it improves compliance sufficiently to achieve the optimal effect in clinical practice. The last line of Table 3 shows the maximal price for the intervention if it is valued at the threshold cost per QALY of SEK 600,000. These calculations assume that if the patient stops the drug (non-persistence), there are no further intervention costs but if the drug is taken irregularly (reduced compliance), full intervention costs are incurred and physician visits and bone density measurements are unaffected.

Table 3 Simulations of the importance of compliance for cost-effectiveness, resulting in a reduced fraction of benefit

	Base case: no previous vertebral fracture		
	No treatment	Treatment	
Total costs	278,056	279,471	
Incremental cost	1415		
QoL	8.96	9.04	
Incremental QoL	0.08		
Life years gained	12.00	12.05	
Incremental life years gained	0.05		
Cost per QALY gained	17,445		
Cost per LY gained	28,743		
	FOB		
	80%	50%	30%
Total costs	*279,739*	*279,967*	*280,170*
QoL	*9.02255*	*8.99801*	*8.98188*
Cost per QALY gained comp to no treatment	25,061	48,025	88,979
Premium absolute price (same cost-effectiveness)	683	1100	(1795)
Premium absolute price (intervention threshold)	832	1262	1545

FOB, fraction of benefit; LY, life-year; QALY, quality-adjusted life-year; QoL, quality of life
Costs converted from SEK to Euros (1 SEK=€0.1088)

Conclusions

Poor compliance with osteoporosis therapies is common, appears within the first months of initiating therapy and is associated with higher fracture rates. The compliance threshold below which anti-fracture efficacy declines is unknown. Poor compliance is a major challenge in contemporary therapeutics because its causes are not known and there are no known clinical features that identify individuals likely to be poor compliers. Factors other than lack of treatment may contribute both to the poor compliance and to the poorer outcomes suffered by these individuals. Less frequent dosing and monitoring of compliance are both associated with better compliance and lower fracture rates but the benefits are still below the high levels considered necessary to achieve optimal anti-fracture efficacy. Given these limitations, close monitoring of compliance and persistence with osteoporosis therapies should be an obligatory duty in clinical care.

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