Implementing adherence to osteoporosis treatments

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Summary

At present chronic diseases are of crucial importance for all health services in the Western World for both their epidemic prevalence and the fact that they absorb a growing proportion of health service financial resources. Osteoporosis has clinical and public health importance because osteoporotic fractures are one of the most common causes of disability and an important contributor to medical costs in many regions of the world. Increased longevity has resulted in the emergence of age-related fragility fractures as a major public health problem. Today several classes of effective drugs are available for osteoporosis. However, these drugs to be effective, need to be taken long-term. In the case of BPs data have shown that nearly 70% of patients on a daily, and almost 60% on a weekly treatment, stop taking medication before the end of 1 year. A poor adherence is associated to an increased probability of fractures with consequent higher likelihood of hospitalisation and higher costs. Since reasons for nonadherence may depend on individual beliefs and circumstances the strategy to improve adherence should be tailored according to the individual patient. These findings underline the key role played by the physicians, above all GPs, in a strategy to improve adherence which now could be supported by the availability of new drugs and innovative administration routes.

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Consequently, also in their capacity to reduce other indirect costs such as hospitalisation, rehabilitation and the necessity for other drugs for relapses. On the other hand, the efficacy of medications used to treat chronic diseases is often reduced by a poor adherence of patients to medications. Adherence is defined as the range of behaviours shown by an individual in response to medical or any other health advice. Therefore, adherence is a general term encompassing all aspects of persistence, compliance and primary non-adherence. Compliance is defined as the extent to which a patient acts in accordance with the prescribed interval and dose as well as dosing regimen. Persistence indicates the duration of the therapy and depends on the ability of the patients to continue the assumption of drugs for the entire length of time prescribed without any prolonged interruption which could interfere with the efficacy. Finally, the term primary non-adherence is used if patients are prescribed a drug and never used the prescription. Adherence is, therefore, crucial in order to achieve the benefits of a drug. For example, an inadequate adherence to a therapy with statins in hypercholesterolemic patients may be responsible for an increased number of myocardial infarctions with consequent extra costs.

Moreover, for many treatments there is a threshold level below which no results can be expected, therefore in these cases the drug simply represents a cost without any benefits (1, 2). Adherence in the setting of osteoporosis has been shown to be just as problematic, if not more, than that in other chronic diseases (2-5).

Osteoporosis is a systemic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and consequently, an increased fracture risk (6). The fact that the osteoporosis is mostly asymptomatic may mean that patients find it difficult to appreciate that treatment is necessary or to understand its benefits. Osteoporosis has clinical and public health importance because osteoporotic fractures are one of the most common causes of disability and an important contributor to medical costs in many regions of the world (7). 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 (8). These fractures are associated with an increased morbidity and mortality that imposes a huge healthcare burden on the community, with an estimated annual cost of €30 billion in Europe and $17 billion in the USA (9, 10). The development of bone mineral density (BMD) testing, portable quantitative ultrasound technology and improved guidelines to define at risk populations have allowed cost-effective targeting of treatment for those subjects most likely to benefit, avoiding needless exposure to treatment of those at low risk of sustaining a fracture. 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 (11).

The data on the efficacy of treatments for osteoporosis have been derived from phase III clinical trials with fragility fractures as a primary end-point. However, the results seen in a trial setting may not apply in a “real life” situation when adherence is
taken into account. In fact adherence observed in clinical trials is likely to be higher than in clinical practice, which in the context of health economic analysis would yield lower benefits of therapy and potentially overestimate cost-effectiveness when using clinical trial data on adherence and efficacy (9).

In a recent review E. Seeman et al. reported the 2 major impediments which threaten efforts to reduce the public health burden of fractures. Firstly, most individuals with fragility fractures remain undiagnosed and untreated, and secondly, among individuals identified as being at risk of fracture, over 50% are either poorly compliant or poorly persistent with treatment within 12 months (3).

Today several classes of effective drugs are available for osteoporosis. However, these drugs to be effective, need to be taken long-term. The difficulty is that the majority of people stop taking drugs within 1 year and many individuals fail to tell their general practitioner that they have stopped treatment. In the case of BPs data have shown that nearly 70% of patients on a daily, and almost 60% on a weekly treatment, stop taking medication before the end of 1 year (12). In this latter study, irrespective of whether the biphosphonate dosage was daily or once weekly, there was a rapid drop-off in prescription refills (non persistence) during the first 3 months (12). Another study found that the persistence of a patients is rapidly reduced in the first months of therapy and one patient in five stops treatment within 6 months (13). In the above mentioned studies the evaluation of persistence was based on the presence of gaps in drug therapy exceeding a defined time interval, e.g. 30 days. However, the persistence generally overestimates the adherence because it does not consider compliance.

At present the medication possession ratio (MPR) has become a standard method of evaluating adherence and is calculated as percentage of days of drug supply versus days of follow-up. However, it should be noted that this definition does not provide information about how consistently prescriptions were refilled, whether the drug was taken according to instructions or even whether it was taken at all (3). However, concerning osteoporosis, MPR is the better studied parameter and is directly connected to the capacity of drugs to reduce fracture risk. A study based on the analysis of a Canadian health service database found that a high compliance with BPs (defined as MPR > 80%) during 2 years of follow-up was associated with 18.7% fewer fractures than poor compliance (MPR < 80%) (14). In another study, carried out on 35537 women prescribed a BP, Siris et al. analyzed fracture probability across the full range of possible MPR and found that compliant women (MPR > 80%) had a 21% lower fracture risk overall than non compliant women (15). Moreover, in women receiving BPs the probability of sustaining a fracture began to decrease only above MPR levels of around 50% and continued to decline with improving compliance up to 90-100% (15). Poor compliance has also been associated with lower reduction of bone turnover markers and smaller increments in BMD (16, 17).

Another study has reported that in osteoporotic women persistence and compliance with bisphosphonate therapy were associated with lower direct costs for non-osteoporosis and osteoporosis-related fractures in patients admissions and outpatient visits (18). Therefore, a poor adherence is associated to an increased probability of fractures with consequent higher likelihood of hospitalisation and higher costs. In the case of the biphosphonates, if they are taken incorrectly or not taken long-term, the patient will not receive the full benefit of the treatment. Analysis of prescribing information in the US has shown that the relative risk of fracture is 26% lower among compliant versus non-compliant patients, and 21% lower in persistent versus non-persistent patients (19).

**Causes of poor adherence in osteoporosis**

In osteoporotic patients, similarly to other chronic diseases, adherence is poorer when symptoms are minimal. In fact among patients with a given chronic disease, a higher level of disease activity is associated with better adherence (20). Studies evaluating the possible influence of age on adherence yielded conflicting results and those of both younger age (<65 years) and older age (>65 years) have been reported as being more or less predictive of better adherence (3, 20).

However, elderly patients could have a higher incidence of symptoms or ailments that may be interpreted as side effects by patient or physician and lead to premature cessation of therapy or be more prone to developing contraindications such as reduced renal function (21). Moreover, many elderly osteoporotic patients are taking multiple medications for different diseases and this is considered a common cause of reduced adherence. Some studies have reported that a prescription of antosteoporotic drugs by a specialist may be associated with better adherence compared to prescription by a general practitioner (22).

Moreover, a recent prescription database study from the Netherlands has revealed a significantly increased risk of non-compliance with oral bisphosphonates in women with a greater number of comedinations (23). Also the scarce knowledge of the patient about the chronic nature of osteoporosis and the necessity to not interrupt the treatment could be an obstacle for the teaching of a good adherence. Other causes of poor compliance include the cost of the medication and the fear of side effects particularly following reports in the media about safety concerns; an example of this has been recently represented by the many interruptions of treatments with bisphosphonates following alarming media reportages of news about ONJ.

However, these putative causes do not explain satisfactory the problem of the poor adherence to antosteoporotic treatments. In fact, Solomon et al. using the claims data from over 40000 patients found that the common predictors of poor compliance such as advanced age, co-morbidity, greater numbers of therapiies etc. accounted for only less than 10% of the variance in compliance (24). Therefore the crucial point is that no patients or disease characteristics reliably predict compliance and persistence (3).

**Strategies for improving adherence**

Given the aging population and the burden of osteoporosis, interventions designed to improve the adherence and reduce the risk of fractures are of great importance. However, improving patient adherence to treatment for chronic disease, such as osteoporosis, represents a complex and difficult challenge for several reasons. Firstly, literature data indicate that fewer than half of interventions designed to improve adherence in chronic diseases were associated with statistically significant improvements in medication adherence (25, 26). Secondly, the lack of data concerning the cost-effectiveness of strategies for improving compliance and persistence in osteoporosis. In fact the savings produced by the fractures prevented could be offset by the cost of the interventions considering that recent studies have found that in another chronic disease, that is hypertension, the patient centred intervention to improve adherence are not cost-effective (27).

However, the simulations based on data derived from the Swedish population indicate that high adherence is likely to be associated with added value for the health-care system (2). Recently the same Swedish Authors have reported that from a health economic perspective, high adherence is particularly important when treating high risk populations such as those with...
a previous fracture (2). A recent pharmaco-economic analysis carried out in Italy by the European House Ambrosetti has reported that by treating patients at high risk for recent hip fracture with zoledronic acid (5 mg i.v.) which guarantees a 100% adherence, a reduction of fractures by 50% could be expected. This choice, if adopted, could produce for the National Health Service a saving of 4-times that of cost of acquisition and administration of the drug (28).

Several strategies for improving adherence to osteoporosis medications have been proposed. In particular, less frequent dosage regimens with biphosphonates improves adherence. In fact, some important studies have found better adherence with weekly regimens, compared to daily dosing (29). Nevertheless, these studies have reported that also with the weekly regimens the adherence after 1 year remained poor and little more than 50% (29).

In another study by Cooper et al. the proportion of osteoporotic patients persisting with treatment at 6 months was 58.6% with monthly ibandronate versus 38.6% with weekly alendronate (30). However, in this latter study the higher persistence with ibandronate could have been the result of a patient support programme (e.g. a monthly telephone reminder provided for the ibandronate only group).

Several studies have reported that densitometric or biochemical tests cause a modest improvement in adherence. In fact in a recent study wich involved patient recall of BMD values, correct understanding of densitometric readings was found to be associated with better adherence to therapy in patients with low BMD (31). Moreover, the IMPACT study showed that reinforcement of osteoporosis treatment using bone turnover data in women treated with daily biphosphonate therapy was associated with fewer fractures (31, 32).

Finally, calendar blister-packs and pill organizers can improve adherence, particularly when combined with general advice from an healthcare professional about the modalities of drug administration. Also the effects of educational materials and leaflets on compliance have been reported to be marginal (3, 20).

In a recent systematic literature review of the interventions to improve adherence and persistence with osteoporosis medication no clear trends regarding successful intervention techniques were identified (33). Nevertheless this latter review has reported that the most efficacious interventions shared one important characteristic: the interaction between study subjects and health care professionals (33). Therefore, the improvements of adherence in osteoporotic patients should be based on the following keypoints:

– early identification of patient with low compliance and persistence;
– definition of a shared management strategy with the objective of improving patients adherence;
– to apply such standard strategies to all patients in order to avoid risks of interruption or suspension of the therapy.

A proposal for an improved adherence

Considering that at present no better method yet exists for improving adherence, a possible solution could be an integrated method which profits from the points of strength of each individual health service.

Since one of the strong points of the Italian Health Service is the capillary distribution of primary care facilities, these may well represent the ideal stepping off point for adherence evaluation and improvement. In this setting adherence to osteoporosis treatment could be primarily evaluated by a simple questionnaire for compilation by the patients aided by a nurse on the occasion of a visit either requested by the patient or within an interventional program (Table I). Any eventual difficulty on the part of the patient to adequately adhere to the osteoporosis therapy would then be discussed with the doctor. The proposed algorithm could be useful in the evaluation of the reasons for nonadherence and lead to the finding of possible solu-
tions in each individual patient (Table II). Doubtless patient are becoming more active in seeking information on medications and need support from their health care providers to interpret this information in order to make decisions that affect adherence. On the other hand since reasons for nonadherence may depend on individual beliefs and circumstances the strategy to improve adherence should be tailored according to the individual patient. These findings underline the key role played by the physicians, above all GPs, in a strategy to improve adherence which now could be supported by the availability of new drugs and innovative administration routes.

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