

Assessment and Potential Determinants of Compliance and Persistence to Antiosteoporosis Therapy in Italy

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Osteoporosis has become a clinical and public health concern because osteoporotic fractures are one of the most common causes of disability and reduced quality of life, and an important contributor to medical costs in many regions of the world.¹ Several medications are currently available for the prevention and treatment of osteoporosis.² However, the effectiveness observed in trials may not be applicable to daily practice, where 50% to 80% of patients discontinue bisphosphonate use in the first year of therapy.^{3,4} Moreover, noncompliance with bisphosphonates has also been reported to be a frequent issue, with rates varying from 35% to 65% of medication possession ratio.⁴ The full benefits of medications for osteoporosis cannot be reached if compliance is low: poorly compliant patients have a greater risk for fractures than patients who adhere to their prescribed therapy,⁵ resulting in higher healthcare use and costs.⁶

The aim of this study was to investigate compliance and persistence with antiosteoporosis drugs (AODs) in a sample of new users and to assess the influence of potential determinants.

METHODS

Data Source

Data used for this retrospective pharmacoepidemiological study were retrieved from the health service databases of the Local Health Units (LHUs)—provincial-level divisions of the Regional Health Authority—of Bergamo (Lombardy Region, Northern Italy), Avezzano-Sulmona, Chieti, Lanciano-Vasto, Teramo (Abruzzo Region, Southern Italy), Avellino, Benevento, Caserta, Napoli Nord, Salerno (Campania Region, Southern Italy), with a total population of about 5.5 million people, entirely covered by the National Health Service (NHS).

Objectives

To analyze adherence to antiosteoporosis drugs (AODs) and to assess the influence of patient-related and drug-related factors.

Study Design

Observational, retrospective study.

Methods

Data on prescriptions for AODs from 2007 through 2008 were retrieved from administrative databases of 10 Italian local health units. Key measurements included compliance and persistence at 1 year. Multivariate regression analyses were performed to estimate adjusted risk ratios for compliance less than 80% and adjusted hazard ratios for no persistence.

Results

Of 40,004 new patients (89.9% women, mean age 69.8 years), 84.0% were treated with bisphosphonates and 74.6% of administration regimens were weekly. Overall, 75.1% of patients had suboptimal levels of compliance and 84.7% were not persistent; almost one-third had only 1 prescription. In regression analyses, younger age, change of drug, and concomitant corticosteroid therapy were significantly associated to compliance and persistence in both genders. In women, weekly and monthly regimens reduced the risk for poor compliance (sex-adjusted relative risks 0.729 [0.697-0.762], 0.846 [0.817-0.876], respectively) and no persistence (sex-adjusted hazard ratios 0.591 [0.541-0.646], 0.508 [0.461-0.560], respectively) compared with a daily regimen.

Conclusions

In our study, 75% of subjects had discontinuous treatment and inadequate drug supply. Age and frequency of administration were strongly associated with adherence. Improvement is urgently needed, and occasional prescriptions represent the main target.

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Prescription data contain dispensed drug name (commercial and international common denomination), Anatomical Therapeutic Chemical (ATC) classification category, dose, number of packs, and date of dispensation. We used the demographic database to retrieve demographic information about patient (gender and age). In compliance with Italian law on privacy, Health Authorities converted patient personal codes to anonymous codes.

Data Selection

AIFA, which is the Italian Medicines Agency and national authority responsible for drug regulation in Italy, has approved 3 bisphosphonates (alendronate, ibandronate, and risedronate) and 4 other drugs (raloxifene, teriparatide, strontium ranelate, and parathyroid hormone) for the treatment of osteoporosis. Oral bisphosphonates are available for daily (alendronate, risedronate), weekly (alendronate, risedronate), or monthly (ibandronate, risedronate) dosing. The Italian government grants reimbursement for AODs in cases of osteoporosis diagnosed by computerized bone mineralometry (T score less than -4 , or less than -3 in high-risk patients), previous vertebral fractures, or chronic therapy with corticosteroids in subjects older than age 50 years.

Patients were included in this analysis if they received a prescription of AODs between January 1 and December 31, 2007. A retrospective analysis covering the period from January to December 2006 was performed to identify new users, excluding subjects who had been prescribed any osteoporosis treatment during the 12-month period prior to the index prescription. The first claim for an AOD during the study period was considered the patient's index date. We also obtained information about any prescription of corticosteroids during the period of 2006 to 2008. Each patient was followed up prospectively for 1 year. Subjects were classified into treatment groups based on the study drug first received.

Outcome Measures

To evaluate treatment compliance and persistence in our cohort, according to International Society for Pharmacoeconomics and Outcomes Research (ISPOR) definitions,^{7,9} the length time with drug available for each refilled prescription was calculated using specific Defined Daily Doses (DDDs).¹⁰ Switching products was not considered an interruption.

Take-Away Points

- Osteoporosis/osteoporotic fractures are common causes of disability and important contributors to medical costs in many regions of the world.
- Poor compliance to antiosteoporosis drugs (AODs) is one of the major issues in the management of osteoporosis and in the prevention of fractures.
- Compliance to AODs is inadequate, both in men and in women, largely due to the high percentage of occasional users.
- Among nonpersistent subjects, one-third restarted therapy after a lapse and one-fifth had medication for at least 80% of the time.
- The frequency of therapeutic regimen is a major influencing factor, as daily regimens are associated with poorer compliance.

Compliance (adherence) was measured as medication possession ratio (MPR), calculated as the total number of days of drug supplied in the observation period divided by the total number of days in the observation period (365), calculated as a percentage. Optimal compliance with therapy was defined by MPR of at least 80%.

Persistence was quantified by the number of days covered by a drug from initiation to discontinuation of therapy. Discontinuation occurred when the period between the end of the coverage of a prescription and the date of the refill was longer than the permissible gap of 30 days.^{11,12} Patients with at least 1 discontinuation episode were considered nonpersistent, even if they subsequently restarted treatment. A sensitivity analysis was performed in order to determine the influence of the duration of the permissible gap on the results.

Statistical Analysis

MPR was described by mean values and by distribution of patients across MPR classes. Persistence rates were evaluated using Kaplan-Meier survival analysis. Heterogeneity tests across groups were undertaken using the unpaired student's *t* test or a 1-way analysis of variance (ANOVA) for continuous variables, and χ^2 test for categorical measures, as appropriate. The impact of some sociodemographic and clinical variables on MPR was estimated using multivariate Poisson regression analysis (dependent variable: MPR <80%). As persistence can change over time, we used a Cox proportional hazards model (dependent variable: nonpersistence). Both regression analyses were adjusted for LHUs. All analyses were performed using SPSS 19.0 (SPSS Inc, an IBM Company, Chicago, Illinois).

RESULTS

We identified 40,004 new users of AODs in 2007: 35,956 women (89.9%, mean age [standard deviation] 69.8 years [11.2]), 4048 men (mean age [SD] 69.6 years [13.9]).

■ **Table 1.** Patients With Prescriptions of Antiosteoporosis Therapy: Characteristics of Prescriptions

	Women	Men	Total
Antiosteoporosis Drugs, n (%)			
Alendronic acid	10,728 (29.8)	1486 (36.7)	12,214 (30.5)
Alendronic acid + cholecalciferol	5754 (16.0)	667 (16.5)	6421 (16.1)
Risedronic acid	11,054 (30.7)	1209 (29.9)	12,263 (30.7)
Ibandronic acid	2511 (7.0)	193 (4.8)	2704 (6.8)
Strontium ranelate	5281 (14.7)	442 (10.9)	5723 (14.3)
Raloxifene	492 (1.4)	37 (0.9)	529 (1.3)
Teriparatide	122 (0.3)	14 (0.3)	136 (0.3)
Parathyroid hormone	14 (0.0)	0 (0.0)	14 (0.0)
Generics	2183 (6.1)	247 (6.1)	2430 (6.1)
Daily administration	6499 (18.1)	835 (20.6)	7334 (18.3)
Weekly administration	26,946 (74.9)	3020 (74.6)	29,966 (74.9)
Monthly administration	2511 (7.0)	193 (4.8)	2704 (6.8)
Changes			
Change of drug	3726 (10.4)	288 (7.1)	4014 (10.0)
Change of frequency of administration	2290 (6.4)	222 (5.5)	2512 (6.3)

Of those, 1792 subjects were 50 years or older and on chronic corticosteroid therapy: 1403 women (3.9%) and 389 men (9.6%).

Characteristics of prescriptions are reported in **Table 1**. Alendronic acid was the most commonly prescribed drug (with or without colecalciferol, 45.8% women and 53.2% men), followed by risedronic acid and strontium ranelate. Antiosteoporosis therapy was mainly administered weekly (97.2% of all prescriptions of only alendronic acid and 96.6% of all prescriptions of risedronic acid). Generics were used by 6.1% of both women and men. The switch to another drug was more frequent than the change of administration regimen (10.0% vs 6.3%).

Compliance is reported in **Table 2**. Although suboptimal in 75.1% of our total sample, compliance was better for women. More than 70% of subjects had already interrupted their treatment after 6 months (**Figure**).

At 1 year, persistent women and men were 15.9% and 10.1%, respectively. In these groups, mean compliance was about 100%. Of the nonpersistent population, females (87.7%) and males (92.8%) had suboptimal compliance; about one-third of nonpersistent women and half of nonpersistent men had only 1 prescription in the study period (**Table 3**). Excluding these subjects, mean MPR levels were 64.3% in women and 58.1% in men. On the other hand, 46.2% and 29.2% of nonpersistent women and men, respectively, showed at least 1 prescription after the interruption (**Table 3**). The sensitivity analysis with a permissible gap of 60 days showed a persistence rate of 40.5%.

Table 4 reports adjusted risk ratios for suboptimal compliance and shows that female subjects younger than 50 years and those 75 years or older were at higher risk of suboptimal compliance, while weekly or monthly administrations (women only), change of drug or of frequency of administration, and concomitant use of corticosteroids were associated with a lower risk of noncompliance. Similar patterns can be seen in the adjusted hazard ratios for nonpersistence (**Table 4**).

DISCUSSION

Osteoporotic fractures represent one of the most common causes of disability and are associated with enormous healthcare expenditure. Although several specific therapies are available, accumulating evidence suggests that these agents are underused in clinical practice.¹³ Moreover, even in subjects undergoing therapy, the management of osteoporosis is difficult because of poor compliance.⁵

Several studies showed that a significant proportion of female patients stopped their treatment within 6 months of initiation and more than half did so within 1 year.^{4,14} In addition, observational studies, although showing wide variations, reported high rates of suboptimal adherence.¹⁵⁻¹⁸ McCombs and colleagues reported a mean MPR of 68%, 1-year persistence rates of 24.2%, and mean lengths of persistence of 170 days for bisphosphonates.¹⁹ Downey and colleagues observed a 12-month prevalence

of optimally compliant patients (MPR $\geq 80\%$) of less than 60%, with persistence rates of 20%.¹⁵ Results of previous studies are not always directly comparable to ours due to a number of methodological differences such as the population selected, the definition of compliance and persistence, the duration of follow-up, analytical techniques used, and differences in settings (populations, practices, and healthcare systems).²⁰ Nonetheless, our findings are consistent with data from other studies, highlighting the widespread problem of poor adherence to antiosteoporosis therapy.

In our study, mean MPR was less than 50%; the optimal compliance rate was 25%; and proportion of persistent subjects was about 15%. These values are mainly the consequence of the high percentage of subjects with only the first prescription (almost 1 out of 3 patients with only 1 prescription in the observed year), a finding particularly relevant in the male cohort (48%) and in younger subjects (53% among subjects < 50 years). Evaluation of the adherence in patients with at least 2 prescriptions showed significantly higher values (mean MPR was 64.3% in women and 58.1% in men).

As AODs are characterized by side effects (gastrointestinal, musculoskeletal, neurological) and transient symptoms that adversely affect the quality of life of the patient, the properties of these drugs may be responsible, at least

■ **Table 2.** Compliance With Antiosteoporosis Therapy

	Women	Men	Total
Compliance			
MPR, mean \pm SD	47.84 \pm 36.61	34.79 \pm 34.15	46.52 \pm 36.58
MPR classes, n (%)			
<50%	20,261 (56.3)	2943 (72.7)	23,204 (58.0)
50-80%	6410 (17.8)	447 (11.0)	6857 (17.1)
$\geq 80\%$	9285 (25.8)	658 (16.3)	9943 (24.9)

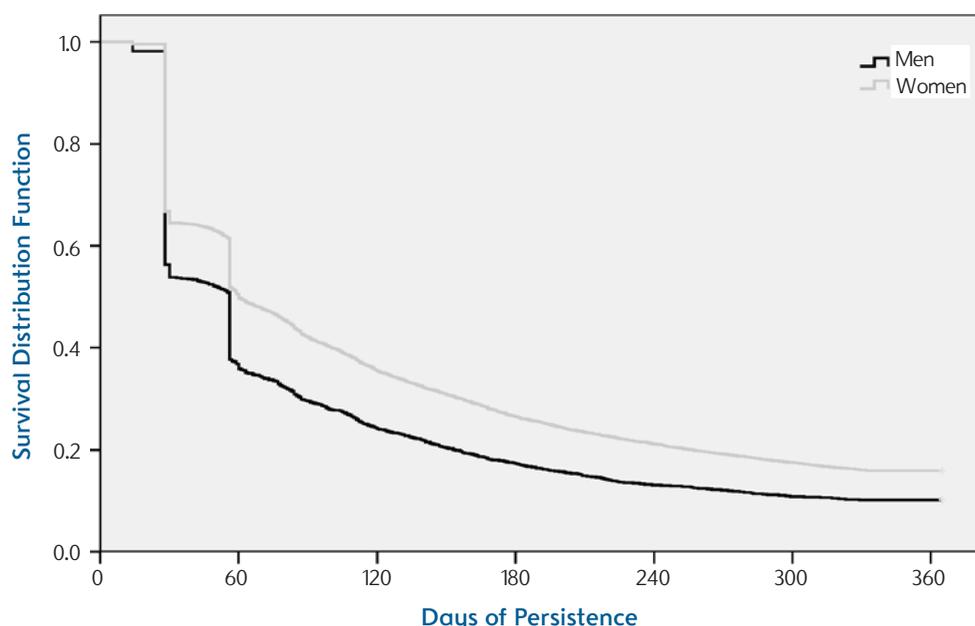
MPR indicates medication possession ratio; SD, standard deviation.

in part, for the observed large proportion of users with only 1 prescription.²¹

The simple distinction between compliant subjects and those exhibiting suboptimal compliance, as well as that between persistent and nonpersistent subjects, provides only a rough description of patient attitude toward drug use, and is strongly influenced by the choice of analysis parameters (an analysis performed with a permissible gap of 60 days showed a persistence rate of 40.5%). In fact, among nonpersistent subjects, 12% had the medication available for more than 80% of the time, thus becoming part of the compliant group despite the presence of occasional therapeutic gaps. Therefore, the proportion of subjects with a discontinuous treatment and insufficient drug supply during 1 year decreased to 75% of the total cohort. These are the patients who may derive a lower-than-expected benefit from therapy.

Indeed, it should be noted that nonpersistence, as defined in this and other studies, is not necessarily equiva-

■ **Figure.** Kaplan-Meier Curve Proportion of Patients Who Interrupted the Antiosteoporosis Therapy



■ **Table 3.** Persistence to Antiosteoporosis Therapy

	Women	Men	Total
Persistence			
Persistent patients, n (%)	5711 (15.9)	408 (10.1)	6119 (15.3)
Patients with MPR \geq 80%, n (%)	5578 (97.7)	396 (97.1)	5974 (97.6)
Nonpersistence			
Nonpersistent patients, n (%)	30,245 (84.1)	3640 (89.9)	33,885 (84.7)
Days of persistence, mean \pm SD	83.63 \pm 74.35	67.44 \pm 63.21	81.89 \pm 73.40
MPR, mean \pm SD	37.68 \pm 30.27	27.28 \pm 26.87	36.56 \pm 30.10
MPR classes, n (%)			
<50%	20,261 (67.0)	2943 (80.9)	23,204 (68.5)
50-80%	6277 (20.8)	435 (12.0)	6712 (19.8)
\geq 80%	3707 (12.3)	262 (7.2)	3969 (11.7)
Patients with 1 prescription, n (%)	10,738 (35.5)	1934 (53.1)	12,672 (37.4)
Patients who restarted therapy, n (%)	13,988 (46.2)	1063 (29.2)	15,051 (44.4)
MPR indicates medication possession ratio; SD, standard deviation.			

lent to permanent treatment discontinuation, as patients may lapse and then resume treatment after a “drug holiday” of variable duration. Actually, most publications that have examined persistence to osteoporosis pharmacotherapy have considered only the initial treatment episode. However, an underreported finding is that many patients who discontinue pharmacotherapy return to treatment after a variable gap, a percentage ranging between 30% and 50% of nonpersistent subjects.^{22,23} In our study, 46% of nonpersistent women and 29% of nonpersistent men showed at least 1 prescription after the first gap. It is possible that these drug-free intervals could have been avoided through closer monitoring of these subjects by their physician.

Previous studies were all conducted using female cohorts, and thus compliance and persistence data in men are scant. In a retrospective chart-review study of male veterans, Hansen and colleagues observed optimal compliance in 59% of patients.²⁴ Our study adds data showing that compliance and persistence rates in men were lower than those estimated in women, mainly due to a greater proportion of subjects with only 1 prescription. In men, as reported in the literature, osteoporosis is a prevalent problem that is underrecognized and undertreated, and morbidity and mortality following a fracture are also greater than they are for women.²⁵ From this perspective, the observed low levels of adherence have even more clinically relevant implications, requiring more attention by physicians, especially in this population.

A few studies have investigated factors influencing nonadherence, identifying side effects, age, and therapeutic

regimen as main determinants.^{11,26-29} In our regression analyses, age was a major determinant of poor adherence and nonpersistence, as both younger age and older age increased risk, probably due to a reduced perception of adverse outcomes from osteoporosis^{30,31} (which has low prevalence in people under age 50 years) and to the increased comorbidity and concomitant treatments at older ages (which may lead practitioners and patients to favor other therapies).^{31,32}

A major perceived problem with oral bisphosphonates is the inconvenience of the regimen, and the association between complex drug regimens and compliance is well established.³³ Several studies showed that less frequent dosing regimens significantly improved levels of both compliance and persistence.³⁴⁻³⁷ This was confirmed in our female sample, supporting a great possibility of improvement from new formulations with delayed administration frequency.

In our analyses, the presence of a therapy change has been shown to reduce the risk of nonadherence and nonpersistence. This evidence may suggest the switch as an indicator of further attention by the physician (to counteract the onset of adverse effects or to meet the patient’s needs), but we should consider that switching to another brand may result in the accumulation of drug units that are not used, which can lead to skewed levels of compliance.

Data about patients who were prescribed bisphosphonates because of chronic corticosteroid therapy are scarce. A study by Curtis and colleagues evaluated persistence and compliance to bisphosphonates at 2 years among corticosteroid users and reported a mean MPR of 73%.³⁸ In our study, compliance levels within corticosteroid therapy

■ **Table 4.** Adjusted Risk Ratios for Compliance <80% and Adjusted Hazard Ratios for Nonpersistence

	Compliance <80%				Nonpersistence			
	Women		Men		Women		Men	
	aRR	CI	aRR	CI	aHR	CI	aHR	CI
Age <50 years ^a	1.127	(1.099-1.157)	1.044	(1.005-1.085)	1.312	(1.234-1.394)	1.252	(1.109-1.415)
Age ≥75 years ^a	1.053	(1.040-1.066)	1.008	(0.981-1.037)	1.125	(1.099-1.152)	0.996	(0.929-1.067)
Use of any bisphosphonate ^b	0.998	(0.964-1.034)	1.187	(1.103-1.278)	1.234	(1.134-1.362)	0.790	(0.667-0.936)
Use of generics	0.992	(0.963-1.021)	0.926	(0.861-0.996)	0.965	(0.918-1.014)	0.917	(0.795-1.058)
Weekly administration ^c	0.729	(0.697-0.762)	1.047	(0.955-1.149)	0.591	(0.541-0.646)	0.905	(0.780-1.049)
Monthly administration ^c	0.846	(0.817-0.876)	1.066	(0.992-1.145)	0.508	(0.461-0.560)	0.900	(0.732-1.107)
Change of drug	0.900	(0.871-0.930)	0.900	(0.819-0.989)	0.902	(0.875-0.949)	0.845	(0.715-0.999)
Change of frequency of administration	1.003	(0.963-1.044)	0.888	(0.791-0.996)	0.959	(0.900-1.023)	0.750	(0.616-0.914)
Use of corticosteroids	0.900	(0.866-0.936)	0.870	(0.816-0.928)	0.841	(0.791-0.893)	0.713	(0.634-0.802)

Both regression analyses were adjusted for LHU (Local Health Unit)

aHR indicates adjusted hazard ratio; aRR, adjusted risk ratio; CI, confidence interval.

^aAge 50-74 years as reference.

^bVersus other anti-osteoporosis drugs.

^cDaily administration as reference.

were poor (mean MPR 56.4%), although higher than those of other patients (mean MPR 46.1%), and in regression analyses, the use of corticosteroids significantly reduced the risk of suboptimal compliance and of nonpersistence. It is likely that these patients are more aware of the risk of fractures and the importance of antiosteoporosis therapy.

The results of our study should be considered within the context of the study's limitations, mainly related to the use of administrative registry as a data source. Although this database allows access to information on a large number of patients gathered in real-world conditions and repeated dispensing over regular intervals is a good proxy for actual compliance and persistence to treatment, pharmacy claims do not guarantee the real consumption of medications, nor do they reflect the actual timing or manner of use. In addition, the administrative database does not capture drugs taken during hospitalization and use of over-the-counter calcium and supplements including vitamin D, so we did not cover all antiosteoporosis interventions. Moreover, data on many important clinical variables that may influence compliance and persistence are not available.

On the other hand, the absence of exclusion criteria specific for age, pathology, or concomitant treatment allowed us to evaluate the AOD utilization profile of an unselected population in the general practice setting. The enrollment of both genders into the study provided information about prescriptive patterns and adherence and persistence to therapy also in the male population. In addition, we extended our observation to all medica-

tions recommended for osteoporosis treatment by Italian guidelines.

Overall, our data underscore the urgent need to improve the use of antiosteoporosis drugs, and suggest some priorities for intervention to improve compliance and persistence. First, both patients and doctors should be more aware that, after the decision to start a pharmacologic therapy, this cannot be interrupted; and that a scheduled, close follow-up is crucial, at least during the initial months of therapy, to reduce drop-out rate after the first prescription. Second, indications to minimize side effects should be offered to the patients whenever these drugs are prescribed. The risk/benefit ratio for younger and older patients should also be expressed. Finally, weekly or monthly regimens should be the preferential choice. The results of such improvement strategies could be easily monitored using the administrative databases, as showed by the current study.

CONCLUSIONS

This study confirms that compliance and persistence to antiosteoporosis drugs is suboptimal in everyday practice, with short periods of persistence and lengthy gaps in therapy, and with 75% of treated patients probably getting no benefit or only partial benefit from therapy. To address these issues, a strategy to detect first prescriptions without any refill should be implemented (such as automated alerts close to the end of drug availability after a prescription is filled), along with adequately planned follow-up

to monitor treatment effectiveness and compliance, and selection of a drug regimen that can help patients be more compliant with therapy. This is an example of how administrative databases, when available, can be used to monitor drug use and to identify the areas in which improvement is needed to increase compliance and persistence to therapy.

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