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ORIGINAL ARTICLE

One and two-year persistence with different anti-osteoporosis medications: a retrospective cohort study

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Abstract

Summary Adherence to anti-osteoporosis medications is poor. We carried out a cohort study using a real-world population database to estimate the persistence of anti-osteoporosis drugs. Unadjusted 2-year persistence ranged from 10.3 to 45.4%. Denosumab users had a 40% lower risk of discontinuation at 2 years compared to alendronate users.

Purpose The purpose of this study was to estimate real-world persistence amongst incident users of anti-osteoporosis medications.

Methods This is a retrospective cohort using data from anonymised records and dispensation data (www.sidiap.org). Eligibility comprised the following: women aged ≥50, incident users of anti-osteoporosis medication (2012), with data available for at least 12 months prior to therapy initiation. Exclusions are other bone diseases/treatments and uncommon anti-osteoporosis drugs ($N < 100$). Follow-up was from first pharmacy dispensation until cessation, end of study, censoring or switching. Outcomes are 2- and 1-year persistence with a permissible gap of up to 90 days. Persistence with alendronate was compared to other bisphosphonates, strontium ranelate, selective oestrogen receptor modulators, teriparatide and denosumab. Cox models were used to estimate hazard ratios of therapy cessation according to drug used after adjustment for age, sex, BMI, smoking, alcohol drinking, Charlson comorbidity index, previous fractures, use of anti-osteoporosis medication/s, oral corticosteroids and socio-economic status.

Results A total of 19,253 women were included. Unadjusted 2-year persistence [95% CI] ranged from 10.3% [9.1–11.6%] (strontium ranelate) to 45.4% [43.1–47.8%] (denosumab). One-year persistence went from 35.8% [33.9%–37.7%] (strontium ranelate) to 65.8% [63.6%–68.0%] (denosumab). At the end of the first year and compared to alendronate users, both teriparatide and denosumab users had reduced cessation risk (adjusted HR 0.76, 95% CI 0.67–0.86 and 0.54, 95% CI 0.50–0.59 respectively) while at the end of the second year, only denosumab had a lower risk of discontinuation (adjusted HR 0.60, 95% CI 0.56–0.64).

Conclusions Unadjusted 2-year persistence is suboptimal. However, both teriparatide and denosumab users had better 1-year persistence and only denosumab had 2-year better persistence compared to alendronate users. Unmeasured confounding by indication might partially explain our findings.

Keywords Cohort study · Medication adherence · Osteoporosis · Primary health care

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Introduction

Regardless of the medical condition studied, adherence to the medications recommended is essential for successful disease control. Persistence is an important matter particularly in osteoporosis given that higher persistence rates have been associated with further reductions in hip and overall fracture risk [1, 2].

Despite this evidence, poor medication adherence is still considered a major issue. Low persistence rates have been extensively reported by both prospective and retrospective studies [3–7]; nearly 50% of patients do not follow their prescribed treatment regimen with early discontinuation of most of the therapies ranging from 50 to 78% [8–10].

Persistence is not only low but also seriously decreases from the first to the second year [11] and up to the fifth year of treatment [3].

In the last few years, a newly commercialised anti-osteoporosis drug (denosumab), which was not included in the aforementioned studies, has proved to have higher persistence rates compared to other anti-osteoporosis therapies (73–84%) [12–15] compared to other intravenous (i.v.) (27%) and oral bisphosphonates (28%) [7, 16].

Therefore, the aim of this study is to estimate the 1- and 2-year persistence and risk of discontinuation with each of the pharmacological treatments available in primary care (including denosumab) for post-menopausal osteoporosis in Catalonia (Spain) amongst incident users of such drugs between January and December 2012, using real-world data.

Methods

Study design and setting

We conducted a population-based cohort study using routinely collected data from de-identified primary care electronic medical records in the *Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària* (SIDIAP) database (http://www.sidiap.org).

Data source/measurements

The SIDIAP database contains electronic medical records from general practitioners and primary care nurses in 274 primary care practices for 5.8 million people in Catalonia (80% of the total population), and comprises extensive information on drug utilization (dispensation date/s, Anatomical Therapeutic Chemical (ATC) code/s and number of daily defined doses (DDDs) purchased) through linkage to the regional community pharmacy invoice data and clinical diagnosis using ICD-10 codes [17].

Participants

Eligible subjects were women of at least 50 years old initiating and purchasing at least 56 daily defined doses (DDDs) of any the following drugs: oral bisphosphonates (ATC M05BA subcodes), strontium ranelate (ATC M05BX03), selective oestrogen receptor modulators = SERMs (ATC G03XC), teriparatide (ATC H05AA02) or denosumab (ATC M05BX04) between 1 January and 31 December 2012 and for whom there was available data for at least 12 months prior to that first dispensation (i.e. index date).

The following exclusion criteria were applied: (1) use of the same drug during the 12 months prior to the index date; (2) history or concomitant incidence of malignant disease (ICD-10 codes: C00-C97 or D00-D49) or use of anti-neoplastics (ATC classes: L19), aromatase inhibitors (ATC L02BG) or cytostatic hormones (ATC classes L2) 12 months prior to the index date; (3) history or concomitant incidence of Morbus Paget (ICD-10 codes: M88) or HIV infection (ICD-10 codes: B20-B24) 12 months prior to index date or (5) drugs with less than 100 users eligible in the study which were also excluded for statistical power issues.

Follow-up

Each patient was studied from at least 12 months prior to the index date (run-in/wash-out period) until end of follow-up, which is defined as the earliest of death or end of data availability, switching or treatment cessation.

Study outcomes

The primary outcome of interest in this study was 2-year persistence with each of the study drugs, with 1-year persistence being a secondary outcome. For those drugs that have two or more different dosing frequencies available (e.g. daily, weekly and monthly for risedronate), persistence was estimated separately for each dosing frequency. Patients were assumed to be persistent with any of the analysed drugs, when a new pack of the analysed drug was dispensed within 90 days (maximum permissible gap) after the end of days' supply from the previous prescription. In this analysis, a different number of days per pack dispensed were used according to the national medicine catalogue and the estimated number of daily defined doses (DDDs) extrapolated from the World Health Organization ATC/DDD catalogue: 28 days per pack dispensed were considered for daily and weekly BP, strontium ranelate, selective oestrogen receptor modulators and teriparatide; 30 days per pack dispensed for monthly BPs; and 182 days per pack dispensed for denosumab.

A sensitivity analysis was carried out extending the permissible gap to 180 days in order to capture any variations in drug persistence.

Both 1- and 2-year persistence with each of the studied drugs were compared to that amongst users of the recommended first-line therapy (weekly alendronate), defined as the reference group.

Statistical methods

Survival analyses were performed where the study outcome was time from index date (treatment initiation) to 2-year (primary) or 1-year (secondary outcome) cessation or censoring for each drug user group. In this survival analysis, failure (the event) was defined as non-persistence with each drug of interest, irrespective of whether the patient terminated treatment completely or restarted treatment after the permissible gap. For this analysis, censoring was considered at end of follow-up, death or date of treatment switching (to an alternative anti-osteoporosis medication). The survival probability (i.e. persistence estimate) at 1 and 2 years was presented with 95% confidence bands.

Kaplan-Meier estimates of cumulative incidence of therapy discontinuation stratified by osteoporosis drug used were plotted. In order to account for potential confounders, multivariable Cox regression models were fitted adjusting for a list of pre-specified confounders as assessed at index date: age, gender, body mass index, smoking, alcohol drinking, Charlson co-morbidity index, previous number of fractures (0, 1, 2 or ≥3), previous use of anti-osteoporosis medication/s, socio-economic status (measured using the ecologic MEDEA socio-economic scale [18]) and use of oral corticosteroids. Hazard ratios (HR) and 95% confidence intervals for risk of discontinuation according to drug use were estimated, using weekly alendronate (the most commonly dispensed anti-osteoporosis medication in our setting) as the reference group.

Multiple imputations with chained equations (MICE) were used to impute variables with missing values (body mass index, smoking, alcohol drinking and socio-economic status) in the multivariable regression models. All the statistical analyses were carried out using STATA SE for Mac V.12.0.

Sample size/power

For the primary study outcome—accepting an alpha risk of 0.05 and in a two-sided log-rank test, and assuming 50% persistence at 2 years for alendronate users (reference group)—754 subjects in the alternative/comparison (other than alendronate) group and 3762 alendronate users are required to ensure 95% power to detect as significant a HR ≤80%. A 10% dropout rate was anticipated for this estimation.

Table 1 Baseline characteristics (n = 19,253)

Variable	Level	N (%)
Age	50–<65	6400 (33.24)
	65–<75	6154 (31.96)
	75–<80	3217 (16.71)
	+80	3482 (18.09)
BMI	<25	4830 (25.09)
	25–<30	6138 (31.88)
	30–<35	3212 (16.68)
	+35	1207 (6.27)
	Missing	3866 (20.08)
Smoking	Non-smoker	15,010 (77.96)
	Smoker	1310 (6.8)
	Former smoker	1115 (5.79)
	Missing	1818 (9.44)
Alcohol drinking	Low risk	12,705 (65.99)
	Moderate	2795 (14.52)
	High risk	78 (0.41)
	Missing	3675 (19.09)
Socio-economic status[a]	Rural	3142 (16.32)
	U1	3832 (19.9)
	U2	3250 (16.88)
	U3	3099 (16.1)
	U4	2851 (14.81)
	U5	2296 (11.93)
	Missing	783 (4.07)
History of osteoporosis	Yes	11,024 (57.26)
Secondary osteoporosis	Yes	598 (3.11)
Number of falls	0	18,859 (97.95)
	1	382 (1.99)
	≥2	12 (0.06)
Bone loss medication[b]	Yes	13,655 (70.92)
Switcher[c]	Yes	6452 (33.51)
Previous calcium/vitamin D supplement user	Yes	10,594 (55.03)
Osteoarthritis	Yes	6866 (35.66)
Hypertension	Yes	8633 (44.84)
Type 2 diabetes	Yes	2040 (10.6)
COPD	Yes	682 (3.54)
Peripheral artery disease	Yes	160 (0.83)
Coronary artery disease	Yes	675 (3.51)
Stroke	Yes	760 (3.95)
Previous osteoporotic fracture[d]	0	14,653 (76.11)
	1	3406 (17.69)
	≥2	1194 (6.2)

BMI body mass index, *COPD* chronic obstructive pulmonary disease

[a] Measured at a census section level using the MEDEA index: values go from U1 being the least to U5 representing the most deprived areas

[b] Bone loss medication: corticosteroids, hypnotics, anti-depressant drugs, anti-epileptic drugs, hypoglucemiant drugs, anti-coagulant drugs, aromatase inhibitors, proton-pump inhibitors

[c] Switcher: previous user of alternative anti-osteoporosis medication in the 1 year before index date

[d] Any fracture except skull, face and digits

Results

Participants and baseline characteristics

A total of 19,253 patients were identified as incident users of any of the studied drugs between 1st January and 31st December 2012. Baseline characteristics of these patients are

Table 2 One- and 2-year persistence per drug

	1 year				2 years			
	n	%	95% CI	*N*	*n*	%	95% CI	*N*
Overall	9060	47.02	46.32, 47.73	19,267	5087	26.40	25.78, 27.03	19,267
Raloxifene	208	45.22	40.6, 49.89	460	117	25.43	21.52, 29.67	460
Bazedoxifene	443	48.47	45.18, 51.76	914	245	26.81	23.96, 29.80	914
Teriparatide	351	57.54	53.51, 61.5	610	115	18.85	15.82, 22.19	610
Alendronate	5223	47.75	46.81, 48.69	10,938	3159	28.88	28.03, 29.74	10,938
Ibandronate	450	40.36	37.46, 43.31	1115	214	19.19	16.92, 21.63	1115
Risedronate	328	33.4	30.45, 36.45	982	169	17.21	14.90, 19.72	982
Strontium ranelate	872	35.8	33.89, 37.74	2436	251	10.30	9.12, 11.58	2436
Denosumab	1183	65.8	63.55, 67.99	1798	817	45.44	43.12, 47.77	1798

n number of persistence patients, *%* percentage of persistent patients over *N*, *95% CI* binomial exact 95% confidence interval, *N* number of patients-drug-frequency

reported in Table 1. Overall, most women included were under 75 years old, had a previous diagnosis of osteoporosis (57%) and were using bone loss medication (71%) and calcium/vitamin D supplements (55%).

Two-year persistence with anti-osteoporosis medications (primary outcome)

Kaplan-Meier (unadjusted) analyses confirmed that denosumab users had the highest persistence at the end of the second year of treatment (45.44% [95% CI 43.12 to 47.77]), followed by alendronate (28.88% [95% CI 28.03 to 29.74]) users (Table 2 and Fig. 1). Incidence rates (IR) of therapy discontinuation in the first 2 years after therapy initiation ranged from 39.12/100 person-years [95% CI 36.75 to 41.65] amongst denosumab users to 106.8/100 py [95% CI 102.44 to 111.40] amongst users of strontium ranelate (see Table 3 for full details and all study drug/s).

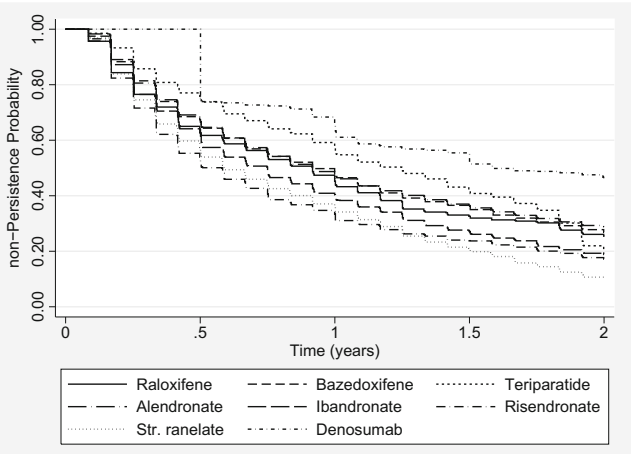

Fig. 1 Kaplan-Meier (unadjusted) analyses confirmed that denosumab users had the highest persistence at the end of the second year of treatment (45.44% [95% CI 43.12 to 47.77]), followed by alendronate (28.88% [95% CI 28.03 to 29.74]) users

Multivariable (Cox) models confirmed that compared to alendronate users—reference group—2-year cessation risk was significantly lower for denosumab users, even after adjustment for pre-identified confounders: adjusted HR 0.60 [95% CI 0.56 to 0.64]. Conversely, ibandronate, risedronate and strontium ranelate users had an increased risk of cessation compared to alendronate users: adjusted HR of 1.27 [95% CI 1.19 to 1.37], of 1.46 [95% CI 1.36 to 1.57] and of 1.61 [95% CI 1.53 to 1.68] respectively. No significant differences in 2-year risk of cessation were found for raloxifene, bazedoxifene and teriparatide users compared to those using weekly alendronate (see Fig. 2).

One-year persistence with anti-osteoporosis medication

When analysing the estimates of persistence by drug (Table 2), denosumab, teriparatide and bazedoxifene users reported the highest persistence (65.8%, 95% CI 63.55 to 67.99; 57.54%, 95% CI 53.51 to 61.5; and 48.47%, 95% CI 45.18 to 51.76 respectively). In contrast, risedronate and strontium ranelate users had the lowest persistence (33.4%, 95% CI 30.45 to 36.45 and 35.8%, 95% CI 33.89 to 37.74 respectively).

Incidence rates (IR) of therapy discontinuation were higher amongst users of risedronate and strontium ranelate. Conversely, those taking denosumab had the lowest IR of therapy discontinuation compared with the rest of anti-osteoporosis medications (Table 3).

Figure 3 reports the estimated adjusted risk of discontinuation at the end of the first year compared with weekly alendronate. After adjusting for potential confounders, women who were prescribed denosumab

Table 3 Incidence rate (100 person-years) of therapy discontinuation

	1 year				2 years			
	Non-persistent (*n*)	Person-year at risk	IR	95% CI	Non-persistent (*n*)	Person-years at risk	IR	95% CI
Overall	10,207	13,545.57	75.35	73.91, 76.83	14,180	20,339.12	69.72	68.58, 70.87
Raloxifene	252	315.31	79.92	70.64, 90.42	343	469.93	72.99	65.66, 81.14
Bazedoxifene	471	646.64	72.84	66.55, 79.72	669	976.08	68.54	63.54, 73.94
Teriparatide	259	473.97	54.65	48.38, 61.72	495	727.79	68.01	62.28, 74.28
Alendronate	5715	7705.31	74.17	72.27, 76.12	7779	11,733.10	66.30	64.84, 67.79
Ibandronate	665	738.01	90.11	83.51, 97.22	901	1047.46	86.02	80.58, 91.82
Risedronate	654	587.84	111.25	103.05, 120.12	813	824.41	98.62	92.06, 105.63
Strontium ranelate	1564	1524.57	102.59	97.63, 107.80	2185	2045.41	106.82	102.44, 111.40
Denosumab	615	1546.81	39.76	36.74, 43.03	981	2507.57	39.12	36.75, 41.65

IR incidence rate, *95% CI* 95% confidence limit

reported the lowest risk of cessation compared to weekly alendronate users (adjusted HR 0.54 [95% CI of 0.50 to 0.59]), followed by those using teriparatide (adjusted HR 0.76 [95% CI 0.67 to 0.86]. Conversely, users of ibandronate, risendronate and strontium ranelate had an increased risk of 1-year therapy cessation.

Sensitivity analysis: 180-day gap permitted

A sensitivity analysis was carried out to determine the persistence at the end of the second year with a permissible gap between prescriptions of 180 days. No major differences were found when analysing the drug persistence compared with the previous 90-day permissible gap (data not shown).

Discussion

Key results

In a population-based study using a source population that covers over five million subjects, a total of 19,267 women were identified as incident users of anti-osteoporosis medication between January and December 2012.

Women using denosumab reported the highest 1- and 2-year persistence rates (and the lowest incidence rates of therapy discontinuation): about two thirds and almost half of the women who started denosumab in 2012 were persistent at the end of the first and second years after therapy initiation. This remained significant in multivariable adjusted models: a 46 and 40% significantly lower risk of 1- and 2-year cessation

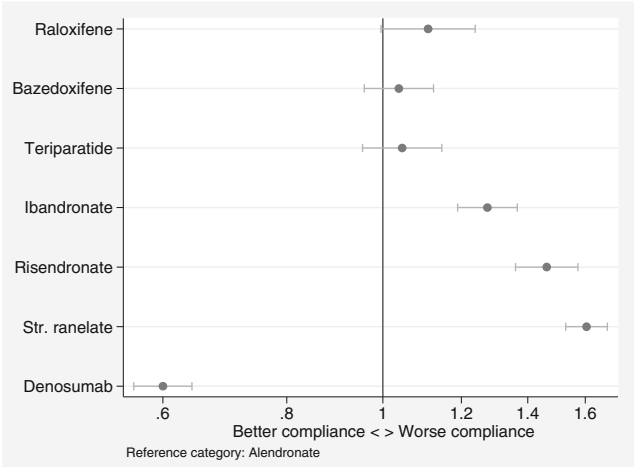

Fig. 2 Adjusted hazard ratio of 2-year drug cessation risk

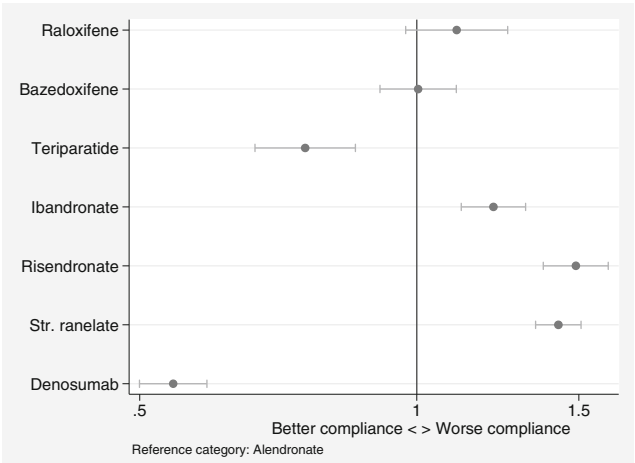

Fig. 3 Adjusted hazard ratio of 1-year drug cessation risk

was observed amongst denosumab users when compared to users of weekly alendronate use respectively. Teriparatide users had also a significantly improved 1-year persistence, but 2-year persistence was similar to that amongst users of weekly alendronate.

In contrast, a significantly higher risk of discontinuation was reported for ibandronate, risedronate and strontium ranelate users at both 1 and 2 years when compared to alendronate users. Regarding the risk of cessation, no differences were found between alendronate and any of raloxifene and bazedoxifene users at 1 and 2 years or for teriparatide users at 2 years; however, persistence with these medications at the end of the second year was lower than those reported for alendronate users.

Comparison with other studies

In our population, overall persistence with anti-osteoporosis therapies was found to be very low; only 47 and 26% persisted with the prescribed treatment at 1 and 2 years respectively.

Drug persistence is an important issue thoroughly analysed in the last years. Low persistence rates with these medications has been previously reported [3–7, 19, 20] in prospective and retrospective studies across the USA and Europe; however, methodological differences regarding the refill gap allowed or the list of drugs included make the cross-study comparison difficult.

As in our study, two other reports analysed the persistence rates allowing the 90-day refill gap between prescriptions [3, 7]. The first study carried out in the Netherlands [3], analysed a total of 8610 subjects of the IADB database and found an overall persistence rate of 67.2%. Differences regarding the definition of the event, such as not counting those subjects who discontinued their treatment for a valid reason, could explain the higher persistence rates found in their study. Although this approach would create a more realistic picture of persistence, the lack of information on drug indication in their databases may have introduced a selection bias, hindering the interpretation of their results assuming that only those subjects who were truly non-persistent would be included. On the other hand, the Grand Study [7], which analysed 4147 women in Germany from the (IMS® DA) database, reported persistence rates of approximately 50% at the end of the first year and of 22% at the end of the second year, which is more in accordance to what we found.

None of the aforementioned studies included denosumab [3, 4, 6, 7, 19, 20] and only one included teriparatide [5]. Reasons for this were either the studies were published before the commercialization of the drug [6, 19, 20] or they included only oral BP [6, 7].

High persistence rates at 1 year have been previously reported for teriparatide [5, 21, 22], which is in line with our results; those subjects using teriparatide reported the second highest persistence and the second lowest risk of discontinuation after denosumab compared to weekly alendronate. The recommended treatment duration for teriparatide goes from 18 to 24 months, which could be the reason underlying the observed high risk of cessation in the second year for this drug.

The persistence of denosumab has been demonstrated in the Denosumab Adherence Preference Satisfaction (DAPS) study. The DAPS study showed that patients treated with denosumab had a significantly high rate of persistence compared with weekly alendronate at 1 year (the adjusted rate ratio of 0.50, representing a 50% relative risk reduction of cessation with denosumab) [23]. In Germany, persistence with denosumab was evaluated using a retrospective analysis on 2386 post-menopausal women; 73% were persistent at 12 months and 58% at 24 months using permissible gap of 60 days [12]. In addition, the real-world persistence to denosumab has been demonstrated in other studies in Hungary and in Sweden, reporting 12-month persistence rates of 84% [13] and 83% [14]. Moreover, prospective observational studies carried out in Austria, Germany and Greece showed that the overall 12-month persistence to denosumab is more than 90% [15]. Our results confirm the higher persistence rates amongst denosumab users and expand what has been previously published comparing denosumab with the rest of anti-osteoporosis medications currently available in primary care: Denosumab users reported not only higher persistence rates but also the lowest risk of cessation at the end of the first and second years, compared to weekly alendronate.

Both teriparatide and denosumab are not considered first-line therapies in the treatment of osteoporosis and are often used to treat subjects in more severe cases. Disease severity, such as already existing osteoporotic fractures, may affect adherence: in a meta-analysis carried out in 2007, the perceived disease severity was strongly associated with a better adherence [24]. Furthermore, higher persistence of anti-osteoporosis medications has been reported (75% at the end of the first year) in patients with fractures [25] compared to persistence rates found in the general population [3–7, 19, 20].

At last, strontium ranelate users reported low persistence rates and an increased cessation which could be partly explained by the regulatory warnings on strontium ranelate safety issued by the European Medicine Agency in 2014, which led to a restriction in use of this anti-osteoporosis drug.

Limitations

The present study is largely descriptive in nature, and as such, it did not allow assessment of causality or drug effects, but to observe and describe associations between drug used and the proposed outcomes (1- and 2-year persistence). Therefore, confounding by indication (i.e. higher disease severity in users of denosumab/teriparatide compared with users of alendronic acid) was likely for the analyses of comparative persistence,

despite attempts to adjust for observed potentially unbalanced variables/baseline characteristics. The lack of information on key markers of disease severity like bone mineral density (which was missing for >99% of the included population) and the fact that drugs with less convenient posology (daily injections of teriparatide) have (in some of our analyses) better persistence than weekly oral alendronate indicate that unresolved confounding might partially explain our findings.

Other limitations also need to be considered: first, treatment dates were based on date of filling the prescription at the pharmacy, which is not necessarily the date of treatment administration. However, misclassification is expected to be at random, which should bias our study results (estimates of comparative persistence) to the null. Secondly, we were not able to differentiate in the analysis between the physician's and the patient's decision to abandon or switch treatment, as both would lead to treatment discontinuation as defined in the proposed study. Furthermore, four covariates had missing information: body mass index, socio-economic status, smoking, and alcohol drinking, and out of these the greatest percentage was for the body mass index and alcohol consumption information. Multiple imputation was used to minimize the effect of missingness in the resulting models. Given that this study is based on primary care data, we were unable to assess the persistence with zoledronic acid and cannot draw any conclusion comparing it to any of the other medications analysed. Finally, we were unable to do further sensitive analysis with shorter treatment gaps (30 or 60 days) given that, in Spain, repeated prescriptions are collected from GP practices every 2 months and hence refill gaps of 2 months or less would not identify therapy cessation.

Generalizability

The study had broad inclusion criteria, which allowed for the inclusion of virtually all post-menopausal women (aged 50 or older at index date) in the target population treated with each of the analysed drugs. The results should therefore be generalizable to the entire population treated with the analysed drugs for osteoporosis in Catalonia (Spain). Generalizability to other jurisdictions is uncertain.

Conclusion

Anti-osteoporosis drugs are commonly used in Catalonia, with a total of 19,267 identified as incident drug users in the year 2012.

Persistence at 1 and 2 years with anti-osteoporosis drugs is overall suboptimal. Despite also having low persistence rates, users of denosumab and teriparatide had a better persistence at the end of the first year compared to users of alendronate (first-line treatment). However, at the end of the second year, only denosumab users had a better persistence compared to users of alendronate.

Finally, bazedoxifene and raloxifene users had equivalent compliance to that observed amongst alendronate users, while users of strontium ranelate, ibandronate and risedronate were the three groups with poorest 1- and 2-year persistence. Unmeasured confounding due to more severe disease (i.e. lower bone mineral density or fragility fractures) amongst users of denosumab and teriparatide might partially explain our findings.

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Compliance with ethical standards

Ethical approval Scientific approval was obtained from the SIDIAP Scientific Committee, and ethics approval was granted by the relevant board (CEIC IDIAP Jordi Gol). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

Conflict of interest DPA's research team has received unrestricted research funding from Bioiberica, Amgen and Servier Laboratoires; DPA's department has received fees for speaker services from Amgen. C.T reports personal fees from Fundació Jordi Gol i Gurina, during the conduct of the study, and personal fees from Boehringer Ingelheim, outside the submitted work. DML reports fees for speaker or consultant services from Amgen, Lilly, MSD and Servier. CR, ASC, CCA and MSA report no conflict of interest.

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