Title	Persistence and compliance to anti-osteoporosis medications in the United Kingdom using the Clinical Practice Research Datalink (CPRD)
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Research Question and Objectives	**Primary Objective** To estimate persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in a real-world setting over 6, 12, 18, 24 month follow-up periods in postmenopausal women. **Secondary Objectives** To estimate persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in a real-world setting over 6, 12, 18, 24 month follow-up periods in postmenopausal women who are treatment-naïve and also in those who are non-naïve treated.
Country(ies) of Study	UK
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1. ABSTRACT

Title

Persistence and compliance to anti-osteoporosis medications in the United Kingdom using the Clinical Practice Research Datalink (CPRD)

Keywords

Osteoporosis, Treatment compliance, Treatment persistence, Oral bisphosphonates, Denosumab

Rationale and Background

Whilst the efficacy of osteoporosis therapies has been demonstrated in multiple randomised clinical trials, poor persistence and compliance to these therapies in the 'real-world' remains a particular problem for patients who receive them. In the UK, a number of studies have evaluated compliance and persistence of anti-osteoporotic therapies. However, the focus has been on commonly prescribed oral bisphosphonates, specifically alendronate and risedronate. All of these studies utilize study periods (up until the end of 2006) where newly introduced medications including ibandronate, zoledronate, denosumab and strontium ranelate (where the dose frequency and mode of administration vary from the traditional bisphosphonate therapy) could not be evaluated

Research Question and Objectives

Primary Objective

To estimate persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in a real-world setting over 6, 12, 18, 24 month follow-up periods in postmenopausal women.

Secondary Objectives

To estimate persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in a real-world setting over 6, 12, 18, 24 month follow-up periods in postmenopausal women who are treatment-naïve and also in those who are non-naïve treated.

Exploratory Objectives

- To describe persistence of denosumab and oral bisphosphonates over 6, 12, 18, 24 months, 3 and 5 years in postmenopausal women
- To describe persistence of denosumab and oral bisphosphonates by dosing frequency (i.e. daily, weekly, monthly) over 6, 12, 18, 24 months, 3 and 5 years in postmenopausal women
- To describe persistence of denosumab and IV bisphosphonates over 6, 12, 18, 24 months, 3 and 5 years in postmenopausal women
- To describe demographic and clinical characteristics in relation to the estimated levels of persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in postmenopausal women
- To describe changes in persistence at key regulatory changes for selected osteoporosis medications

- **Study Design**

A retrospective database analysis of the Clinical Practice Research Data link (CPRD) to evaluate the persistence and compliance of osteoporosis therapies between 2010-2015. Persistence and compliance were evaluated in three cohorts. Patient-level cohorts included all patients who received an osteoporosis medication ('all patients' cohort – cohort 1), or just those who were naïve to prior treatment ('naïve patients' cohort – cohort 2), regardless of the type of treatment received. Persistence and compliance to individual drugs was measured in the 'drug specific' cohort (cohort 3), overall and according to whether they were naïve or not naïve to prior treatment.

- **Setting**

Real world data derived from the UK general practice.

- **Subjects and Study Size, Including Dropouts**

Women aged 50 years and over or women aged 18-50 experiencing a premature (incl. surgery-induced) menopause and who receive at least one prescription for any licensed osteoporosis therapy (oral bisphosphonates, parenteral bisphosphonates, SERMs, denosumab, PTH, strontium ranelate) between January 1st 2010 and December 31st 2015. Total eligible patients were 100,373 patients and after exclusion of those with history of cancer, metabolic bone disease or less than 6 months of follow-up, the final study population was 72,256.

- **Variables and Data Sources**

Clinical risk factors for osteoporosis and osteoporosis therapies by drug class.

- **Results**

Oral bisphosphonates were by far the most common starting treatment (94.7% in the 'all patients' cohort); by contrast, very few patients were prescribed parenteral bisphosphonates (0.6%) or parathyroid hormone (0.5%). The mean age of patients who received strontium (77.0 years), denosumab (76.9 years) or parathyroid hormone (75.6 years), was higher than those receiving bisphosphonates (oral, 73.9 years; parenteral, 73.3 years) or SERMs (68.8 years). Denosumab and parathyroid hormone users were more likely to have a diagnosis of osteoporosis recorded (39.7% and 42.8%, respectively) than the overall study population (29.4%) and were more likely to have a history of fracture (49.8% and 51.4%) than in those receiving other therapies, particularly SERMs (16.1%). The FRAX-calculated 10-year risk of osteoporotic fracture was also higher in patients receiving denosumab (22.45%), strontium

(21.87%) or parathyroid hormone (21.24%) than those receiving other treatments (13.81–19.48%).

Patients in cohorts 1 and 2 were assigned into a drug class based on the medication that they were receiving upon entry into the study. If a patient switched to a different class of osteoporosis medication within the permissible gap (i.e. 30 days in the primary analysis), then they would still be considered persistent. Therefore, in this patient-level analysis, persistence was measured as persistence to overall osteoporosis treatment, and not reported for individual treatments. Persistence to osteoporosis medications declined over time, from 56.1% after 6 months to 31.0% after 24 months and 13.1% at 5 years. Persistence was slightly higher in patients who were treatment-naïve than the overall population for the entire duration of follow up: median duration of persistence to osteoporosis treatment was 8.5 months in the 'all patients' cohort and 12.4 months in the 'naive patients' cohort.

In the drug-specific cohort (cohort 3), patients could contribute multiple records if they discontinued treatment and then resumed treatment with the same or a different class of osteoporosis medication within the permissible gap (i.e. 30 days in the primary analysis). Two different sets of Kaplan-Meier curves were derived: one for the overall population and another separating the populations according to whether they were treatment-naïve or non-naïve. In the overall population analysis, persistence was greater for denosumab than any other therapy; the exception was at 6 months where 100% persistence was observed for parenteral bisphosphonates, which is due to the 1-year frequency of administration for zoledronic acid. Denosumab persistence remained at 50% or above for the first 24 months, whereas apart from the 6-month timepoint for parenteral bisphosphonates (zoledronate), persistence for other medications was below 50% at all time intervals. The median duration of persistence was longest for denosumab (24.0 months), followed by parenteral bisphosphonates (12.0 months), oral bisphosphonates (3.7 months), SERMs (2.5 months), strontium (1.9 months), and PTH (0.9 months).

When comparing the naïve vs non-naïve treated patients in cohort 3, there was a different pattern of persistence depending on the route of administration. Among the orally-administered medications (oral bisphosphonates, strontium, SERMs), persistence was consistently higher in patients who were naive to previous osteoporosis therapy. For example, persistence at 12 months for naive vs non-naive patients was 50.8% vs 19.2% for oral bisphosphonates, 42.2% vs 17.6% for strontium, and 29.7% vs 12.1% for SERMs. In contrast, among the parenterally-administered medications (denosumab, parenteral bisphosphonates, PTH), persistence was higher in patients who were non-naive to previous osteoporosis therapy. For example,

persistence at 12 months for naive vs non-naive patients was 54.7% vs 65.7% for denosumab, and 12.5% vs 26.0% for parenteral bisphosphonates (no naive patients were available at month 12 in the PTH group).

Compliance was measured using the MCR and MPR among patients who were persistent within a given time period. Compliance to therapies was high in all cohorts, and remained generally good for those that started a medication and then remained on it.

- **Discussion**

The study shows that injectable agents also appear to be reserved for older, more severely diseased patients, compared with the oral medications. This is probably reflective of the treatment guidance that was available in the UK over the study period investigated (i.e. oral medications are first choice, then other medications can be given subsequently, depending on response and tolerability to the first-line therapy).

Persistence to most osteoporosis medications remains poor with approximately 50-60% of patients stopping their therapy after 12 – 18 months. The results highlight that few patients persist with treatment long enough to gain its expected benefit, and also that few persist long enough for the National Osteoporosis Guideline Group (NOGG) guideline on medication review (recommending review after 3–5 years of treatment) to be relevant. However, persistence has been improved with the use of longer-acting injectable medications such as subcutaneous denosumab and intravenous bisphosphonates. In accordance with previous studies, persistence to oral therapies declines markedly after the first line of treatment (non-naïve-treated), but with injectable agents persistence was improved after receiving prior therapies.

There are limitations to this study primarily based on the data contained within the CPRD database. However, this study demonstrates that newer injectable agents do tend to have better persistence that oral therapies, and that these will be useful in those patients who may have failed or are unable to tolerate previous treatments.

- **Marketing Authorization Holder(s)**

Amgen Inc.

- **Names and Affiliations of Principal Investigators**