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Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review

F Fatoye, P Smith, T Gebrye, G Yeowell

Department of Health Professions, Manchester Metropolitan University, Manchester, UK

Correspondence to
Professor F Fatoye;
f.fatoye@mmu.ac.uk

ABSTRACT

Objectives This study examined patient adherence and persistence to oral bisphosphonates for the treatment of osteoporosis in real-world settings.

Methods A systematic review was completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Medical Literature Analysis and Retrieval System Online (MEDLINE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine Database (AMED), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) and National Health Service Economic Evaluation Database NHS EED) databases were searched for studies published in English language up to April 2018. Prospective and retrospective observational studies that used prescription claim databases or hospital medical records to examine patient adherence and persistence to oral bisphosphonate treatment among adults with osteoporosis were included. The Newcastle–Ottawa quality assessment scale (NOS) was used to assess the quality of included studies.

Results The search yielded 540 published studies, of which 89 were deemed relevant and were included in this review. The mean age of patients included within the studies ranged between 53 to 80.8 years, and the follow-up varied from 3 months to 14 years. The mean persistence of oral bisphosphonates for 6 months, 1 year and 2 years ranged from 34.8% to 71.3%, 17.7% to 74.8% and 12.9% to 72.0%, respectively. The mean medication possession ratio ranged from 28.2% to 84.5%, 23% to 50%, 27.2% to 46% over 1 year, 2 years and 3 years, respectively. All studies included scored between 6 to 8 out of 9 on the NOS. The determinants of adherence and persistence to oral bisphosphonates included geographic residence, marital status, tobacco use, educational status, income, hospitalisation, medication type and dosing frequency.

Conclusions While a number of studies reported high levels of persistence and adherence, the findings of this review suggest that patient persistence and adherence with oral bisphosphonates medications was poor and reduced notably over time. Overall, adherence was suboptimal. To maximise adherence and persistence to oral bisphosphonates, it is important to consider possible determinants, including characteristics of the patients.

Strength and limitation of this study

► This review only included prospective and retrospective observational studies that derived objective prescription claim data from outside clinical trial settings, to better reflect real-world adherence and persistence to oral bisphosphonates for the treatment of osteoporosis.
► This review was able to derive persistence and adherence data from 89 observational studies performed within 15 different countries,
► The calculation of persistence and adherence across the included studies were heterogeneous. As a result, it was not possible to directly compare these studies via meta-analysis.
► The review did not collect self-reported patient data. This data may have given further insight as to the determinants of persistence and adherence among patients with osteoporosis.

INTRODUCTION

Osteoporosis is a chronic global health condition, characterised by low bone density and bone structure deterioration.[1] About a third of men and more than half of all women experience osteoporosis during their lives.[2] Moreover, evidence suggests that fracture-related mortality rate is higher in men than women.[3] The first sign of osteoporosis is often a fracture of the wrist, hip and spine. Osteoporotic fractures can lead to long-term problems such as chronic pain, long-term disability and even death.[4] The long-term problems of osteoporosis may also lead to a substantial economic burden on individuals, health systems and society. Osteoporosis is a common disease in the USA, and more than 1.5 million osteoporosis-related fractures occur each year.[5] For example, the findings of a study of osteoporosis-related fractures in the USA indicated that patients with a diagnosis of osteoporosis and concurrent fracture ($15,942) had more than two times the annual healthcare expenditure, compared with patients with osteoporosis without a fracture ($6,476).[5] The total cost estimates for the treatment of osteoporosis and subsequent care in the USA was around $17 billion in 2003 and this is expected to increase by

50% in 2025.[6 7] The majority of this cost is spent on acute surgical and medical management, and subsequent rehabilitation.[6]

Bisphosphonate medications for osteoporosis have been shown to increase bone strength and reduce fracture risk and can be administered orally or intravenously across a wide range of doses and dosing intervals.[8 9] Bisphosphonate treatments such as etidronate, alendronate, ibandronate, risedronate and zoledronic acid are able to prevent vertebral fractures more than placebo.[10] Prevention can be classified as primary or secondary. Primary prevention attempts to protect individuals against the onset of osteoporosis, whereas secondary prevention treats individuals living with the disease.[11] Treatments such as alendronate, risedronate and other oral medications such as oestrogen can prevent hip fractures more than placebo. Patients treated with alendronate and zoledronic acid had better efficacy in preventing hip fracture. On the other hand, zoledronic acid was reported to lead to an increased risk of adverse events than alendronate and placebo.[12] The clinical issues that should be considered when treating patients with osteoporosis using bisphosphonates include: the choice of which type of bisphosphonates to use, monitoring to assure the medication is taken correctly, determining the time when these medications should be discontinued and the management of their side effects.[13]

Patient persistence and adherence to oral bisphosphonates can be assessed using real-world data. This can be derived from electronic health records, product and disease registries, claims and billing data and data gathered through personal devices.[14] The International Society for Pharmacoeconomics and Outcomes Research defines persistence as the accumulation of time from initiation to discontinuation of therapy.[15] Adherence/compliance was defined as the extent to which a patient acts in accordance with the prescribed interval and dose as well as dosing regimen. Poor persistence and adherence to bisphosphonate therapy can significantly increase the risk of fracture and overall burden of osteoporosis.[12] Thus it is important to quantify the prevalence of this in wider populations and consider potential factors that may influence this, such as patient characteristics.

Although previous systematic reviews have included some real-world data, the studies were not assessed for quality and did not examine the potential determinants of adherence and persistence.[16 17] To the authors' knowledge, there is no contemporary review that focuses on oral bisphosphonate medication adherence and persistence among patients with osteoporosis in the real-world. Understanding patient persistence and adherence to oral bisphosphonates and their determinants may be used to reduce the risk of fractures in the treatment of osteoporosis.[1] Therefore, this current systematic review addresses two objectives. First, it summarises patient persistence and adherence to oral bisphosphonates in real-world settings. Second, it identifies determinants that may affect real-world adherence and persistence.

METHODS

This systematic review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guideline, a technique that addresses the eligibility, data sources, selection of studies, data extraction and data analysis.[18] The review was registered on PROSPERO, with registration number CRD: 42017059894.

Data sources

We searched the Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature, MEDLINE; Database of Abstracts of Reviews of Effects, Health Technology Assessment database and the Centre for Reviews and Dissemination database up to April 2018. The search terms used were persist* OR adher* OR non-adher* OR complian* OR discontinu* OR prescri* OR pattern* OR gap* (TITLE) AND Osteoporo* OR Osteopen* OR (Bone AND loss) OR Alendron* OR Etidron* OR Ibandron* OR Risedron* OR bisphosphonat* (TITLE). All search results were exported into EndNote Web (Thomas Reuter, CA, USA) bibliography software.

Inclusion criteria

Prospective and retrospective observational studies that used prescription claims databases or patient electronic medical records or to investigate persistence and adherence to oral bisphosphonate medications in the treatment of osteoporosis or osteopenia in human adults were included. Eligible studies were required to have an abstract and article published in the English language, within a peer-reviewed source. Studies conducted in any geographical location were permitted. Randomised controlled trials (RCTs), systematic reviews, narrative literature reviews and conference papers were excluded. Further exclusion criteria were as follows; abstract unavailable, studies not yet fully completed, single case studies/reports, observational studies drawing persistence/adherence data from patient or general practitioner survey, prospective studies designed to observe changes in adherence via the introduction of a non-typical intervention or adjunct and studies containing patients aged <18 years.

Study selection

Duplicates were removed electronically and manually. Two independent researchers (PS and TG) were involved in screening the title and abstract of each study. Full-text articles were obtained and were excluded if they did not meet the inclusion criteria. Any disagreement in study selection was resolved through discussion and consultation with other members of the project team (GY and FF), where necessary. During screening, open-label extension studies of RCTs were excluded. It was considered that this design may not generate data that truly reflected a real-world pattern of persistence and adherence. Studies using data from electronic medical records, outside of addition to large-scale databases were also included provided

persistence and adherence data were determined from prescription claims data rather than extracted from supplemental patient interviews, patient-supplied pill counts or subjective questionnaires. The literature search was supplemented by screening the reference lists of included articles for further eligible studies.

Data extraction and study quality assessment

Determinants (factors that may affect or be associated with) persistence or adherence were extracted from eligible studies, including patient characteristics such as age and sex, medication, population location, time-frame of data collection and length of follow-up. The quality of the studies was assessed using the Newcastle–Ottawa quality assessment scale (NOS) for cohort studies.[19] The NOS contains eight items, categorised into three dimensions including selection and comparability. The maximum score of NOS is nine. However, some questions within the NOS were not applicable across the eligible studies dependent on their study design. In this instance, authors determined and adjusted the NOS score to account for this, rating studies only on the number of questions that were applicable and relevant.

Data analysis

A descriptive analysis of extracted results is presented. No meta-analysis was carried out due to heterogeneity of reporting methodologies and calculations of adherence and persistence across studies.

Patient and public involvement

Patients and the general public were not involved in this study.

RESULTS

The literature search identified 540 potential articles, of which 517 were remained after the removal of duplicates. After the titles and abstracts of these publications were screened, 143 references were identified as potentially relevant and retrieved in full text. Of these, 89 were included in review (figure 1). The methodological quality of the included studies is presented (table 1). All the included studies scored between six to eight on the NOS.

The geographical location of the studies included were: USA (n=37), Canada (n=7), UK (n=6), Netherlands (n=6), Denmark (n=5), Italy (n=5), Germany
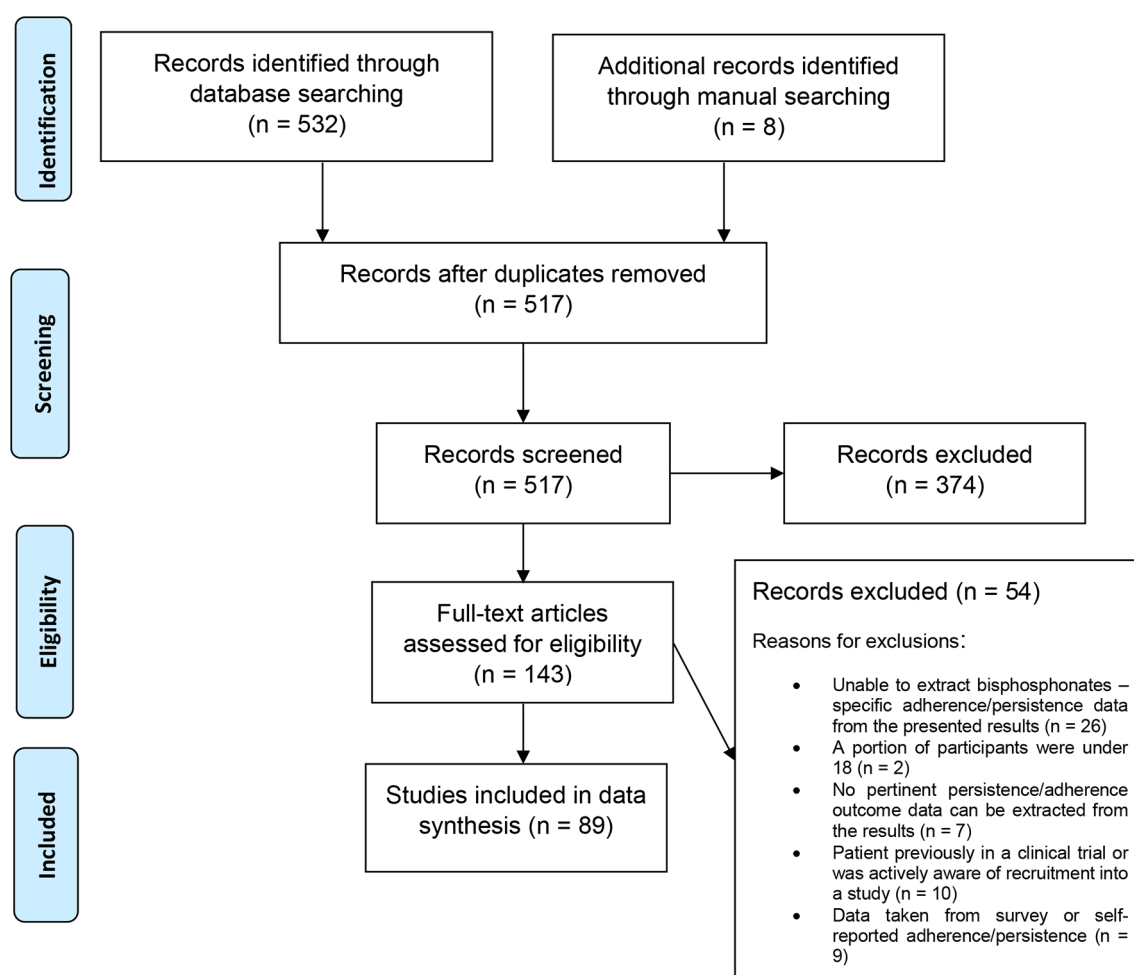
Figure 1 The preferred reporting for systematic reviews and meta-analyses diagram representing the systematic literature search.[94]

Table 1 Summary of studies included in this review

Reference	Type of database	Country	Time frame of data collection	Length of follow-up	Adjusted NOS scores
Abrahamsen[29]	National prescription	Denmark	1995 to 2007	10 years	6/6
Blouin et al[30]	Régie de l'asssurance maladie du Québec	Canada	2002 to 2004	2 years	8/8
Blouin et al[20]	Régie de l'asssurance maladie du Québec	Canada	1998 to 2001 & 2000 to 2004	1 year	6/6
Brankin et al[31]	General practice research database IMS disease analyser	UK	2001 to 2004	1 year	6/6
	Doctors independent network database				
Briesacher et al[32]	MarketScan research databases	USA	2000 to 2004	1 to 3 years	6/6
Briesacher et al[33]	MarketScan commercial claims and encounters and Medicare	N/A	2001 to 2006	1 year	6/6
Burden et al[34]	Ontario drug benefit database	Canada	1996 to 2009	1 to 9 years	6/6
Burden et al[35]	Ontario drug benefit database	Canada	2001 to 2012	1 year	6/6
Cadarette et al[21]	Pennsylvania pharmaceutical assistance contract	USA	1995 to 2005	6 months	6/6
Carbonell-Abella et al[22]	Sistema d'informacio per al desenvolupament de la investigacio en atencio primaria	Spain	2007 to 2010	1 year	8/8
Cheen et al[36]	CITRIX patient record management system and MAXCARE prescription record system, Singapore General Hospital	Singapore	2007 to 2008	2 years	6/6
Cheng et al[23]	Chang-Gung Memorial Hospital, Kaohsiung Medical Centre	Taiwan	2001 to 2007	2 years	8/8
Colombo and Montecucco[37]	Aziende sanitarie locali	Italy	2008 to 2008	34 months	6/6
Copher et al[38]	Administrative claims	USA	2002 to 2006	1 year	8/8
Cotté et al[39]	Thales longitudinal prescription	France	2007 to 2008	1 year	8/8
Cramer et al[40]	De-identified healthcare claims	USA	1997 to 2002	1 year	8/8
Cramer et al[41]	Integrated Healthcare Information Services Inc.	USA	1997 to 2003	1 year	6/6
	General practice research database	UK	2001 to 2005		
	Thales	France	2000 to 2004		8/8
Curtis et al[42]	Linked enrolment, outpatient encounter, pharmacy and procedural billing	USA	2001 to 2004	39 months	
Curtis et al[43]	Unidentified administrative claims	USA	1998 to 2005	3 years	6/6
Curtis et al[44]	Unidentified administrative claims	USA	1998 to 2005	3 years	6/6
Curtis et al[45]	Unidentified administrative claims	USA	1998 to 2005	1 year	6/6
Devine et al[46]	Pharmacy data transaction service data warehouse	USA	2006 to 2008	1 year	8/8

Continued

Table 1 Continued

Reference	Type of database	Country	Time frame of data collection	Length of follow-up	Adjusted NOS scores
Devold et al[47]	Norwegian prescription database	Norway	2005 to 2009	5 years	8/8
Downey et al[24]	National administrative claims	USA	2001 to 2003	1 year	6/6
Dugard et al[48]	An unidentified database of GP records	UK	1996 to 2002	5 years	6/6
Ettinger et al[49]	A large database was accessed through	USA	2002 to 2003	1 year	6/6
Feldstein et al[50]	Undefined health maintenance organisation	USA	1996 to 2006	2.7 years	6/6
Gallagher et al[51]	General practice research database	UK	1987 to 2006	2.3 years	8/8
Gold et al[52]	IMS longitudinal prescription	USA	X to 2005	6 months	8/8
Gold et al[53]	Unidentified pharmacy claims	USA	1996 to 2003	2 years	6/6
Gold et al[54]	IMS longitudinal prescription	USA	1996 to 2003	1 year	8/8
Hadji et al[55]	IMS disease analyser patient	Germany	2004 to 2007	2 years	6/6
Hadji et al[25]	Techniker krankenkasse	Germany	2006 to 2009	2 years	6/6
Hadji et al[56]	IMS disease analyser patient	Germany	2001 to 2010	1 year	6/6
Halpern et al[26]	Unidentified administrative claims	USA	2002 to 2006	18 months	8/8
Hansen et al[27]	Danish national registers	Denmark	1996 to 2006	5.2 years	6/6
Hansen et al[57]	Veteran affairs pharmacy service records	USA	2000 to 2004	2 years	8/8
Hawley et al[58]	Sistema d'informació per al desenvolupament de l'investigació en atenció primaria	Spain	2006 to 2007	6 months	6/6
Hoer et al[59]	Claims database of a statutory sickness fund	Germany	2000 to 2004	2 years	6/6
Ideguchi et al[60]	Yokohama City University Medical Centre	Japan	2000 to 2005	5 years	6/6
Iolascon et al[28]	Unidentified administrative prescription database campania	Italy	2008 to 2010	1 year	6/6
Jones et al[61]	Ontario Drugs Database and Brogan Inc. private payer database	Canada	2003 to 2006	1 year	6/6
Kamatari et al[62]	Pharmacy prescription database	Japan	2000 to 2005	4 years	6/6
Kertes et al[63]	Maccabi healthcare services database	Israel	2003 to 2004	1 year	6/6
Kishimoto and Machara[64]	Platform for clinical information statistical analysis database	Japan	2006 to 2014	8 years	6/6
Lakatos et al[65]	National health insurance fund administration	Hungary	2004 to 2013	2 years	6/6
Landfeldt et al[66]	Swedish prescribed drug register	Sweden	2005 to 2009	4 years	6/6
LeBlanc et al[67]	Kaiser Permanente Northwest	USA	1997 to 2011	5 years	6/6
Li et al[68]	General practice research database	UK	1995 to 2008	5 years	6/6
Lin et al[69]	Unidentified health insurance database	Taiwan	2003 to 2006	1 year	6/6

Continued

Table 1 Continued

Reference	Type of database	Country	Time frame of data collection	Length of follow-up	Adjusted NOS scores
Lo et al[70]	Kaiser Permanente of Northern California	USA	2002 to 2004	1 year	8/8
Martin et al[71]	HealthCore integrated research database		2005 to 2007	3 years	8/8
McCombs et al[72]	Unidentified health insurance company, California	USA	1998 to 2001	1 year	6/6
Modi et al[73]	InVision data mart database	USA	2002 to 2009	1 year	6/6
Modi et al[74]	InVision data mart database	USA	2001 to 2010	2 years	6/6
Modi et al[75]	Humana administrative health claims database	USA	2007 to 2013	1 year	6/6
Netelenbos et al[76]	IMS health longitudinal prescription database	Netherlands	2007 to 2008	1 year	6/6
Olsen et al[77]	The Danish national prescription register	Denmark	1997 to 2006	2 years	8/8
Papaioannou et al[78]	The Canadian database of osteoporosis and osteopenia	Canada	1990 to 2001	3 years	8/8
Patrick et al[79]	Medicare and the Pennsylvania pharmaceutical assistance contract for the elderly	USA	1996 to 2005	6 months	6/6
Penning-van Beest et al[80]	PHARMO record linkage system	Netherlands	2000 to 2003	1 year	6/6
Penning-van Beest et al[81]	PHARMO record linkage system	Netherlands	1999 to 2004	1 year	6/6
Penning-van Beest et al[82]	PHARMO record linkage system database	Netherlands	1999 to 2004	1 year	8/8
Rabenda et al[83]	Belgian national social security institute	Belgium	2001 to 2004	1 year	8/8
Recker et al[84]	NDC health database	USA	2002 to 2003	1 year	6/6
Reynolds et al[85]	Kaiser Permanente Southern California	USA	2009 to 2011	1 year	6/6
Richards et al[86]	Veterans affairs rheumatoid arthritis registry	USA		39.2 months	8/8
Rietbrock et al[87]	General practice research database	UK		1 year	6/6
Roerholt et al[88]	National hospital discharge register and Danish national prescriptions database, Denmark	Denmark	1997 to 2004	9 years	6/6
Roughead et al[89]	Department of veterans' affairs	Australia	2001 to 2007		6/6
Sampalis et al[90]	Ontario ministry of health and long-term care databases	Canada	1996 to 2009	14 years	6/6
Scotti et al[91]	Healthcare utilisation databases, Lombardy	Italy	2003 to 2010	5.3 years	8/8
Sheehy et al[92]	Régie de l'assurance maladie du Québec databases		2002 to 2007	1 year	6/6
Siris et al[93]	MedStat MarketScan commercial claims and encounters and Medicare databases	USA	1999 to 2003	2 years	6/6
Siris et al[94]	The MarketScan commercial claims and encounters and Medicare supplemental and coordinator of benefits databases	USA	2001 to 2008	2.4 years	6/6

Continued

Table 1 Continued

Reference	Type of database	Country	Time frame of data collection	Length of follow-up	Adjusted NOS scores
Soong et al[95]	National health insurance research database	Taiwan	2004 to 2006	1 year	6/6
Ström[96]	Swedish prescribed drug register	Sweden	2005 to 2009	4 years	6/6
Sunyecz et al[97]	Thomson healthcare, MarketScan commercial claims and encounters and MarketScan Medicare, supplemental and coordination of benefits databases	USA	2000 to 2002	3 years	6/6
Tafaro et al[98]	General practitioner databases	Italy	2001 to 2007	300 days	6/6
Van Boven et al[99]	The InterAction database	Netherlands	2003 to 2011	1 year	6/6
Van den Boogaard et al[100]	PHARMO record linkage system	Netherlands	1996 to 2003	3 years	6/6
Wang et al[101]	Centres for Medicare and Medicaid services	USA	2006 to 2010	5 years	6/6
Weiss et al[102]	IMS longitudinal prescription database		2004 to 2006	1 year	6/6
Weycker et al[103]	PharMetrics patient-centric database	USA	1998 to 2003	5.5 years	6/6
Weycker et al[104]	Health alliance plan of Henry Ford Health System	USA	2002 to 2007	27.1 months	6/6
Yeaw et al[105]	PharMetrics patient-centric database	USA	2005 to 2005	1 to 2 years	6/6
Yood et al[106]	Unidentified health maintenance organisation	USA	1998 to 1999	18 months	6/6
Zambon et al[107]	Health services databases of Lombardy	Italy	2003 to 2005	3 years	6/6
Ziller et al[108]	IMS longitudinal prescription database	Germany	2007 to 2009	1 year	6/6

GP, general practitioner; NOS, Newcastle–Ottawa quality assessment scale; N/A, not reported.

(n=5), Japan (n=3), Taiwan (n=3), Spain (n=2), France (n=2) and single studies from Singapore, Norway, Israel, Hungary, Sweden, Belgium and Australia (see table 1). The mean age of patients included within the studies ranged between 53 to 80.8 years and the length of follow-up ranges between 3 months and 14 years. The length of follow-up of the included studies could be stratified to 6 months (n=4), 1 year (n=37), 2 years (n=16) and ≥3 years (n=32).

The medications included in this review as primary or secondary prevention in the treatment of osteoporosis are alendronate, etidronate, risedronate, ibandronate, clodronate, zoledronate, alendronate +vitamin D and risedronate +calcium. Some of the included studies also looked at pamidronate and raloxifene.[20–28] In order to measure the persistence and adherence of patients to these medications the included studies have used different techniques.[20–108] Persistence was measured based on the length of treatment without a gap in refills (table 2). The permissible gap between medication refills the included studies used was typically 30 days, and sometime 60 or

90 days. On the other hand, adherence was measured by calculating the medication possession ratio (MPR),[20 23–25 29 32 33 36–48 50 52 54 55 57 59 64 67 69–71 74–77 81–84 87 90 93–95 97 98 101 104 105 108] and proportion of days covered (PDC).[21 35 79 91 105] MPR means the number of days' supply of medication received divided by the length of the follow-up period.[109]

Persistence

Sixty studies assessing persistence using real-world data from 4 070 739 patients were identified (table 2). The overall mean persistence of oral bisphosphonates at 6 months,[39 40 42 52 58 61 65 68 74 76 78 83 90 92 104] 1 year,[21–25 28 31 34–36 39–42 48 49 51 53 55 56 59–68 70 78 80 83 87 90 92 95 99 100 103 105 108] 2 years[25 27 30 34 36 42 48 53 56 59 60 64–66 68 90 94 100 103] and 3 years ranged from 34.8% to 71.3%, 17.65% to 74.80%, 12.9% to 60.60% and 21.0% to 40.0% respectively (figure 2). The 6 month persistence of ibandronate,[39 52 65 68] alendronate[42 61 65 68 78 92] and risedronate,[39 52 61 65 68 92] ranged from 29% to 57.3%, 45.5% to 79% and 46.8% to 77%, respectively. Thirteen studies reported 1 year persistence data for alendronate (12.6% to 70.1%),[22 24 28 42 62 65 66 68 78 92 99]

Table 2 Persistence data for osteoporosis medications by study

Reference	Medications	Population (mean age)	Length of persistence (days)	Patient persistence		
				6 months	1 year	2 years
Brankin et al[31]	Alendronate, risedronate	15330 (71.7)	233	n/a	55% (weekly regimen), 42.8% (daily regimen)	n/a
Burden et al[34]	Alendronate, etidronate, risedronate	451113 (75.6)	n/a	n/a	63.10%	46.40%
Burden et al[35]	Alendronate, etidronate, risedronate	337329 (75.7)	n/a	n/a	56%*, 66%†	n/a
Carbonell-Abella et al[22]	Alendronate, ibandronate, risedronate	118829 (66.9)	n/a	n/a	14.1% (alendronate daily), 56.5% (alendronate weekly), 35.8% (ibandronate monthly), 7.7% (risedronate daily), 31.2% (risedronate weekly), 40.0% (risedronate monthly)	n/a
Cheen et al[36]	Alendronate, risedronate	798 (68.5)	n/a	n/a	69%*	n/a
Cheng et al[23]	Alendronate	1745 (68.1)	n/a	n/a	57.1%*	41.8%*
Cotté et al[39]	Alendronate, risedronate	2990 (69.9)	169	45.7%*	30.4%*	n/a
Cramer et al[40]	Alendronate, risedronate, ibandronate	2741 (n/a)	196	44.6%* (daily), 58.1%* (weekly)	31.7%* (daily), 44.2%* (weekly)	n/a
Cramer et al[41]	Alendronate, risedronate	2741 (73)	204	n/a	50%‡ (weekly), 38.6%‡ (daily)	n/a
Curtis et al[42]	Alendronate, risedronate	1158 (53)	n/a	51.4%§ (alendronate) 46.8%§ (risedronate)	32.4%§(alendronate), 26.7%b (risedronate)	9.5%§ (alendronate), 5.4%§ (risedronate)
Devine et al[46]	Alendronate, ibandronate, risedronate	22363 (n/a)	189.8* (weekly), 196.3* (monthly)	n/a	n/a	n/a
Downey et al[24]	Alendronate, risedronate	10566 (66.4)	n/a	n/a	21.3% (alendronate), 19.4% (risedronate)	n/a
Dugard et al[48]	Not stated	254 (76.7)	n/a	n/a	74%¶	59%¶
Ettinger et al[49]	Alendronate, risedronate	211319 (n/a)	n/a	n/a	56.7%* (weekly), 39%* (daily)	n/a
Gallagher et al[51]	Alendronate, risedronate	44531 (n/a)	n/a	n/a	58.3%§	n/a
Gold et al[52]	Ibandronate, risedronate	234862 (n/a)	144.3§ (risedronate), 100.1§ (ibandronate)	29%§ (ibandronate) 56%§(risedronate)	n/a	n/a
Gold et al[53]	Alendronate	4769 (n/a)	261*	38%* (daily), 49%* (weekly)	26%* (daily), 36%* (weekly)	16%* (daily), 24%* (weekly)
Gold et al[54]	Ibandronate, risedronate	263383 (66.21)	151.54§ (bandronate) 250.04§ (risedronate)	n/a	18.4%§ (ibandronate), 40%§ (risedronate)	n/a
Hadji et al[55]	Alendronate, clodronate, etidronate, risedronate	4147 (n/a)	145.5*	n/a	27.9%*	12.9%*
Hadji et al[25]	Alendronate, clodronate, etidronate, risedronate	19752 (n/a)	n/a	n/a	26%*	20.1%*

Continued

Table 2 Continued

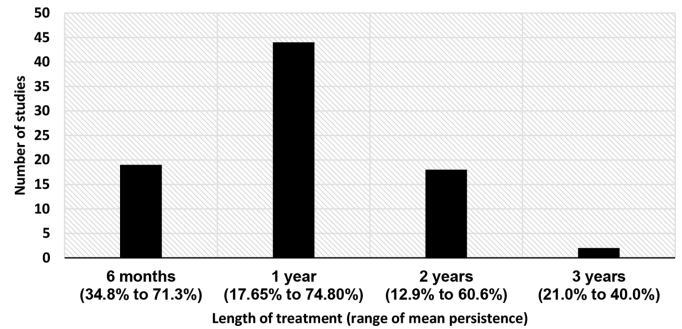| Reference	Medications	Population (mean age)	Length of persistence (days)	Patient persistence		
				6 months	1 year	2 years
Hadji et al[56]	Clodronate, ibandronate, pamidronate, zoledronate	280 (63.2)	n/a	n/a	45.6%§	n/a
Hansen et al[27]	Alendronate, other oral bisphosphonates	100 556	1463** (alendronate) 532.9** (clodronate) 963.6** (etidronate) 1408.9** (ibandronate) 1018** (risedronate)	n/a	n/a	n/a
Hansen et al[57]	Alendronate	198 (71)	n/a	n/a	n/a	28%
Hawley et al[58]	Not stated	21 385 (n/a)	n/a	45.65%	n/a	n/a
Hoer et al[59]	Alendronate, etidronate, risedronate	4451 (n/a)	n/a	71.3%*	47.3%*	14.5%*
Ideguchi et al[60]	Alendronate, etidronate, risedronate	1307 (61.3)	n/a	n/a	74.8%§	60.6%§
Iolascon et al[28]	Alendronate, risedronate, ibandronate	18 515 (68.9)	n/a	n/a	12.6%* (alendronate), 15.8%* (risedronate), 21.6%* (ibandronate)	n/a
Jones et al[61]	Alendronate, risedronate,	62 897 (n/a)	n/a	72%* (alendronate weekly) 71.2%* (risedronate weekly)	56.3%* (alendronate weekly), 54.4%* (risedronate weekly)	n/a
Kamatari et al[62]	Alendronate, risedronate	1274 (74)	n/a	n/a	42.5% * (alendronate), 44.6% * (risedronate)	n/a
Kertes et al[63]	Alendronate, risedronate	4448 (n/a)	216*	n/a	46%*	n/a
Kishimoto and Machara[64]	Not stated	12 230 (59.8)	n/a	n/a	33.2% (daily regimen)	13.0%* (daily), 32.7%* (weekly), 50.4%* (weekly regimen)
Lakatos et al[65]	Alendronate, risedronate, ibandronate	296 300 (68.3)	n/a	50%†† (alendronate), 50% †† (ibandronate), 55% †† (risedronate)	35%†† (alendronate), 30% ††(ibandronate), 42% ††(risedronate)	20%††† (alendronate), 16% ††† (ibandronate), 22% ††† (risedronate)
Landfeldt et al[66]	Alendronate, risedronate	56 586 (71)	n/a	n/a	55%†† (alendronate), 54% †† (risedronate)	38%†† (alendronate), 38%†† (risedronate)
LeBlanc et al[67]	Not stated	14 674 (71)	n/a	n/a	58%¶¶	23%‡‡
Li et al[68]	Alendronate, etidronate, risedronate, ibandronate	66 116 (71.4)	n/a	27%* (alendronate daily), 52.8%* (alendronate weekly), 56.8%* (ibandronate monthly), 37.8%* (risedronate daily), 53.1%* (risedronate weekly)	17.6%* (alendronate daily), 41.3%* (alendronate weekly), 6.5%* (ibandronate monthly), 26.4%* (risedronate daily), 41.1%* (risedronate weekly)	n/a
Lo et al[70]	Alendronate	13 455 (68.8)	378†	40%†	50%†	n/a

Continued

Table 2 Continued

Reference	Medications	Population (mean age)	Length of persistence (days)	Patient persistence		
				6 months	1 year	2 years
McCombs et al[72]	Alendronate, etidronate, risedronate	3720 (69.1)	170	n/a	n/a	n/a
Modi et al[73]	Alendronate, etidronate, risedronate	75 593 (64.4)	115.6*	39.30%*	n/a	n/a
Netelenbos et al[76]	Alendronate, etidronate, ibandronate, risedronate	105 506 (69.2)	n/a	43.10%§§	n/a	n/a
Papaioannou et al[78]	Alendronate, etidronate	1673 (66.8)	n/a	n/a	77.6% (alendronate), 90.3% (etidronate)	70.1% (alendronate), 80.5% (etidronate)
Penning-van Beest et al[80]	Alendronate, risedronate	2124 (71.6)	n/a	n/a	42.9%*	n/a
Rabenda et al[83]	Alendronate	54 807 (n/a)	n/a	58%¶¶	40%¶¶	n/a
Richards et al[86]	Alendronate, risedronate	573 (68.7)	1176§	n/a	n/a	n/a
Rietbrock et al[87]	Alendronate, risedronate	44 531 (71)	n/a	n/a	58.30%	n/a
Roerholt et al[88]	Alendronate, etidronate, ibandronate	6210 (74.7)	474 (alendronate 10 mg), 1350.5 (alendronate 70 mg), 803 (etidronate)	n/a	n/a	n/a
Roughead et al[89]	Not stated	42 885 (80.8)		n/a	n/a	n/a
Sampalis et al[90]	Alendronate, ibandronate, Risedronate	636 114 (72)	n/a	41.0%*	41.0%*	26.6%*
Sheehy et al[92]	Alendronate	32 804 (n/a)	n/a	79%***	65%***	n/a***
Siris et al[93]	Alendronate, risedronate	35 357 (65.3)	n/a	n/a	n/a	20%*
Soong et al[95]	Alendronate	32 604 (72.4)	n/a	48.03%*	17.6%*	n/a
Ström et al[96]	Alendronate, risedronate	36 433 (70.2)	n/a	n/a	51.67%††	n/a
Sunyecz et al[97]	Alendronate, risedronate	32 944 (64.3)	n/a	n/a	n/a	21%*(3 years)
Van Boven et al[99]	Alendronate, etidronate, ibandronate, risedronate	8610 (67.5)	n/a	n/a	48.9%*	40%*(3 years)
Van den Boogaard et al[100]	Alendronate, etidronate, risedronate	14 760 (n/a)	n/a	n/a	43.60%	27.40%
Weiss et al[102]	Alendronate, ibandronate, risedronate	165 955 (67.1)	109*	n/a	n/a	n/a
Weycker et al[103]	Alendronate, risedronate	18 822 (62.2)	n/a	45.5%§(daily), 47.3% § (weekly)	19.2%§ (daily)	3.7%§ (daily), 3.6%§(weekly)
Yeaw et al[105]	Alendronate, ibandronate, risedronate, zoledronate, etidronate, pamidronate	10 268 (56.9)	n/a	56%*	41%†	n/a

Continued

Figure 2 Frequency for reported range of mean persistence per length of treatment.

[108] risedronate (15.8% to 68.0%)[22 24 28 42 54 61 63 65 68 92 100 108] and ibandronate (18.4% to 58.5%)%).[22 28 54 65 68 99 108]

Out of 19 studies,[25 27 30 34 36 42 48 53 56 59 60 64–66 68 90 94 100 103] that reported the 2 year persistence of oral bisphosphonates, more than 70% of them found the proportion of patients persistent to be <30%. A 3 year persistence of 21% and 40% was reported by two studies.[97 99]

Adherence

We identified 55 studies that measured adherence based on real-world data from 4 033 731 patients in different countries (table 3). The minimum length of follow-up period used in the included studies to measure MPR and PDC was 3 months. The 3 month follow-up study reported the proportion of adherent patients to alendronate and risedronate as 72.8% (daily) and 80% (weekly).[80] Few studies reported MPR that ranged between 55.6% and 90% for 6 months follow-up (table 3).[21 52 59 79] Across all studies that reported MPR at 1 year, the proportion of patients adherent to medication varied from 31.7% to 72.0%.[23 24 27 28 32–34 36 38–42 44 46 48 53 59 61 64 69 71 73 74 76 80 84 94 95 105 108]

Across six studies adherence at 2 years was less than that of adherence at 1 year, ranging from 34.5% to 47.9%.[23 32 43 59 71 74] Parallel to this, six studies reported the proportion of patients who achieved MPR ≥80% at 3 years varied between 23% and 47.9%.[29 32 43 44 48 71] Overall, adherence rates to oral bisphosphonates reduced overtime within and across studies.

Determinants of persistence and adherence

Out of the 89 studies, 55 reported at least one potential determinant of persistence and adherence to oral bisphosphonates (online supplementary file 1). The potential determinants of persistence and adherence reported in the studies included geographic residence,[30] prior bone mineral density (BMD) test,[20 30 39 48 70] chronic disease score,[30] hospitalisation,[30 51 80 94] medication type and frequency,[22 24 31 38–43 45 46 49 51–54 63 64 78 80 81 83 86 91 92 97 99 100 102 103 107 108] age,[27 36 38 40 42 46–49 51 53 61 63 69 70 73 76 77 80 81 87 89 91 93 94 99 102 104 107] history of fractures,[36 51 59 72 73 77 81 88 94 103] race/ethnicity[38] and number of co-medication.[40 69 77 88 91 93] In addition to these, glucocorticoid,[43 70 100] gender,[51 60 62 69 76 77 88 92 99] education status,[47 77 86] income,[47] marital status,[47] history of

Table 2	Continued						
				Patient persistence			
Reference	Medications	Population (mean age)	Length of persistence (days)	6 months	1 year	2 years
Ziller et al[108]	Alendronate, etidronate, risedronate	268 568 (63.3)	239.8 hour (alendronate 70mg), 218.7§ (alendronate +vitamin D), 246.4§ (etidronate), 256.4§ (ibandronate 150mg), 190.9§ (residronate)	n/a	44.8% hour (alendronate 70mg), 37.8%h (alendronate +vitamin D), 43.4%h (etidronate), 50.8%h (ibandronate), 30.3%h (residronate)	n/a

*Persistence with no refill gaps ≥ 30 days.
†Persistence with no refill gabs > 60 days.
‡Patient persistence defined as length of time before a refill gap > 30 days.
§Persistence with no refill gaps ≥ 90 days.
¶Persistence was defined as complete cessation or a gap > 12 months.
**Persistence with as no refill gaps > 56 days/8 weeks, n/a means not reported.
††Persistence with no refill gaps > 8 weeks.
‡‡Persistence was defined as the length of time until a refill gap > 3 months.
§§Persistence with no refill gaps > 6 months, n/a means not reported.
¶¶Persistence was defined as length of time without a refill gap > 5 weeks.
***Persistence was defined as length of time until refill gap exceeding 1.5 × prescription length, n/a means not reported.

Table 3 Adherence data for osteoporosis medications

Reference	Medication	Population (mean age)	Compliance, mean MPR		
Abrahamsen[29]	Alendronate	58 674 (n/a)	<5 years	5 to 10 years	>10 years
	Etidronate		Alendronate (92%)	Alendronate (84%)	Alendronate (76%)
	Ibandronate		Etidronate (92%)	Etidronate (89%)	Etidronate (88%)
	Risedronate		Ibandronate (81%)	Ibandronate (75%)	Ibandronate (70%)
	Clodronate		Risedronate (91%)	Risedronate (80%)	Risedronate (75%)
Blouin et al[20]	Alendronate	15 027 (76.6)	69.7%±34.8%		
	Risedronate				
Briesacher et al[32]	Alendronate, risedronate	17 988 (61.4)	At 1 year,	At 2 years,	At 3 years,
			42.9% (MPR ≥80%)	34.5% (MPR ≥80%)	30.6% (MPR ≥80%)
			12.6% (MPR 60% to 79%)	10% (MPR 60% to 79%)	10% (MPR 60% to 79%)
			10.4% (MPR 40% to 59%)	7.7% (MPR 40% to 59%)	7.2% (MPR 40% to 59%)
			13.8% (MPR 20% to 39%)	8.2% (MPR 20% to 39%)	7.8% (MPR 20% to 39%)
			20.4% (MPR <20%)	38.7% (MPR <20%)	44.2% (MPR <20%)
Briesacher et al[33]	Alendronate, ibandronate, risedronate	61 125 (62.1)	At 1 year (monthly medication),	At 1 year (weekly medications)	At 1 year (daily medication)
			49% (MPR≥80%)	49% (MPR ≥80%)	23% (MPR ≥80%)
			11% (MPR 60% to 79%), 11% (MPR 40% to 59%), 13% (MPR 20% to 39%)	14% (MPR 60% to 79%)	8% (MPR 60% to 79%)
			16% (MPR <20%)	9% (MPR 40% to 59%)	11% (MPR 40% to 59%)
				14% (MPR 20% to 39%)	16% (MPR 20% to 39%)
				14% (MPR <20%)	42% (MPR <20%)
Burden et al[35]	Alendronate, etidronate, risedronate	337 329 (75.7)	70%*		
Cadarette et al[21]	Alendronate, risedronate	20 205 (79)	49.8% (PDC ≥80%); 14.5% (PDC 51% to 79%); 35.7% (PDC ≤50%)		
Cheen et al[36]	Alendronate, risedronate	798 (68.5)	78.90%		
Cheng et al[23]	Alendronate	1745 (68.1)	At 1 year; 61.9%	At 2 years, 47.9% (MPR ≥80%)	
			(MPR >80%)		
Colombo and Montecucco[37]	Generic alendronate, branded alendronate	20 711 (73)	69% to 74%		
Copher et al[38]	Alendronate, ibandronate, risedronate	1587 (62.3)	48.70% (95% CI 46.2 to 51.2)		
Cotté et al[39]	Alendronate, risedronate	2990 (69.9)	79.4% (95% CI 78.2 to 80.5) (weekly medications)		
	Ibandronate		84.5% (95% CI 83.1 to 85.9) (monthly ibandronate)		
Cramer et al[40]	Alendronate, risedronate, ibandronate	2741 (n/a)	60.60%		
Cramer et al[41]	Alendronate, risedronate	2741(73)	64%		
Curtis et al[42]	Alendronate, risedronate	1158 (53)	73%		
Curtis et al[43]	Alendronate, risedronate	25 446 (n/a)	At 2 years,		At 3 years,
			Achieved MPR >80% = 29.4%		Achieved MPR >80% = 27.2%

Continued

Table 3 Continued

Reference	Medication	Population (mean age)	Compliance, mean MPR		
			Achieved MPR <50% = 34.9%		Achieved MPR <50% = 39.4%
Curtis et al[45]	Alendronate	101 038 (n/a)	Achieving MPR >80% = 44%		
	Ibandronate, risedronate				
Devine et al[46]	Alendronate, ibandronate, risedronate	22 363 (n/a)	62%		
Devold et al[47]	Alendronate	7610 (66.6)	Achieving MPR ≥80% = 45.5%		
Downey et al[24]	Alendronate, risedronate	10 566 (66.4)	60.7% (alendronate)		
			58.4% (risedronate)		
Dugard et al[48]	Not stated	254 (76.7)	At 1 year,	At 3 years,	At 5 years, achieving MPR ≥80% = 23%
			Achieving MPR ≥80% = 44%	Achieving MPR ≥80% = 42%	
Feldstein et al[50]	Alendronate, ibandronate, risedronate	1829 (72)	60%		
Gold et al[52]	Ibandronate, risedronate	234 862 (n/a)	83.3% (risedronate)	79% (risedronate)	
			78.5% (ibandronate)		
Gold et al[53]	Ibandronate, risedronate	263 383 (66.21)	74.68% (ibandronate)		
			80.15% (risedronate)		
Hadji et al[55]	Alendronate, clodronate, etidronate, risedronate	4147 (n/a)	Achieving MPR ≥80% = 66.3%		
			Achieving MPR <80% = 22.7%		
Halpern et al[26]	Alendronate, ibandronate, risedronate	21 655 (63.3)	At 6 months,		At 18 months,
			76% (commercially insured)		59% (commercially insured)
			68% (Medicare advantage)		53% (Medicare advantage)
Hansen et al[57]	Alendronate	198 (71)	At 12 months,		At 2 years,
			Achieving MPR ≥80% = 59%		Achieving MPR ≥80% = 54%
Hoer et al[59]	Alendronate, etidronate, risedronate	4451 (n/a)	At 6 months,		At 1 year,
			Achieving MPR ≥80% = 58.6%		Achieving MPR ≥80% = 46.25%
Kishimoto and Machara[64]	Not stated	12 230 (62)	At 1 year,		At 5 years,
			38.6% (daily)		20.8% (daily)
			70.6% (weekly)		60.9% (weekly)
			77.7% (monthly)		
LeBlanc et al[67]	Not stated	14 674 (71)	94%		
Lin et al[69]	Alendronate	8936 (74)	60.20%		
Lo et al[70]	Alendronate	13 455 (68.8)	93%		
Martin et al[71]	Alendronate, ibandronate, risedronate	45 939 (59.6)	At 1 year,	At 2 years,	At 3 years,
			58% (alendronate)	48% (alendronate)	42% (alendronate)
			58% (ibandronate)	50% (ibandronate)	46% (ibandronate)
			57% (isedronate)	47% (risedronate)	43% (risedronate)
Modi et al[75]	Alendronate, ibandronate, risedronate	37 886 (74.1)	Achieving MPR ≥80% = 31.7%		
Netelenbos et al[76]	Alendronate	105 506	91%		

Continued

Table 3 Continued

Reference	Medication	Population (mean age)	Compliance, mean MPR		
		−69.2			
Olsen et al[77]	Alendronate, etidronate	47 176 (70.3)	Achieving MPR <50% = 28.4%		
			Achieving MPR 50% to 79% = 11.8%		
			Achieving MPR ≥80% = 59.8%		
Penning-van Beest et al[81]	Alendronate, risedronate	8822 (69.4)	At 3 months,	At 6 months, achieving MPR ≥80%	At 1 year,
			Achieving an MPR ≥80%	Daily = 60.3%	Achieving MPR ≥80%,
			Daily=72.8%	Weekly = 70.8%	Daily = 50.2%
			Weekly=80.0%		Weekly = 64.3%
Penning-van Beest et al[82]	Alendronate, risedronate	8822 (n/a)	Achieving MPR ≥80% = 58%		
Rabenda et al[83]	Alendronate	54 807 (n/a)	64.70%		
Recker et al[84]	Alendronate, risedronate	211 319 (n/a)	54% (daily regimen)		
			65% (weekly regimen)		
Richards et al[86]	Alendronate, risedronate	573 (68.7)	69%		
Sampalis et al[90]	Alendronate, ibandronate, risedronate	636 114 (72)	72%		
Siris et al[93]	Alendronate, risedronate	35 357 (65.3)	Achieving MPR ≥80% = 43%		
Siris et al[94]	Alendronate, ibandronate, risedronate	460 584 (63.6)	53.50%		
Soong et al[95]	Alendronate	32 604 (72.44)	At 1 month,	At 2 months,	At 1 year,
			Achieving MPR ≥80% = 87.6%	Achieving MPR ≥80% = 61.8%	Achieving MPR ≥80% = 28.2%
Sunyecz et al[97]	Alendronate, risedronate	32 944 (64.3)	55%		
Tafaro et al[98]	Alendronate, clodronate, ibandronate, risedronate	6390 (n/a)	53% (daily regimen)		
			70% (weekly regimen)		
Wang et al[101]	Alendronate, ibandronate, risedronate	522 287 (n/a)	Achieving MPR <33% = 41.1%		
			Achieving MPR 34% to 65% = 21.5%		
			Achieving MPR >66% = 37.3%		
Weycker et al[104]	Alendronate, ibandronate, risedronate	644 (65.9)	57%		
Yeaw et al[105]	Alendronate	10 268 (56.9)	*60%		
	Ibandronate				
Yood et al[106]	Alendronate, etidronate	176 (63.3)	70.70%		
Ziller et al[108]	Alendronate	268 568 (63.3)	33% (alendronate 10 mg)		
			57% (alendronate 70 mg)		

*Mean Proportion of Days Covered (PDC).
MPR, medication possession ratio.

upper gastrointestinal problems,[51] tobacco use,[27] rheumatoid arthritis,[62 86] national insurance,[63] hormone replacement therapy,[70] clinical service use,[79] mental disorder,[104] diabetes and co-payments,[102 104] were mentioned as determinants of persistence and adherence. The relationship of these determinants to patients' persistence and adherence to medication is described below.

In the studies that have reported prior BMD test as a determinant factor, patients who have undergone prior BMD test before receiving medications have higher persistence and adherence compared with those who have not.[20 30 39 48 70] Moreover, weekly oral bisphosphonates medication users had significantly higher mean persistence than those daily users.[22 24 31 38–43 45 46 49 51–54 63 64 78 80 81 83 86 91 92 97 99 100 102 103 107 108] Before decreasing at ages 80 and above a number of studies have reported higher persistence and adherence at older ages than younger ages.[27 36 38 40 42 46–49 51 53 61 63 69 70 73 76 77 80 81 87 88 91 93 94 99 102 104 107] Similarly, the number of co-medications being received at baseline was associated with a marginally greater risk of discontinuing.[40 69 77 88 91 93] Compared with male users of oral BP medications, female users were at lower odds of achieving adherence.[51 60 62 69 76 77 88 92 99]

DISCUSSION

This review summarises patient persistence and adherence and their determinants with oral bisphosphonates in the treatment of osteoporosis in real-world settings. A total of 89 studies, undertaken in the USA, Canada, Europe, Asia and Australia were used to collect information on the real-world persistence and adherence with oral bisphosphonates for the treatment of osteoporosis. The analyses of these data suggest that patient persistence and adherence rates to oral bisphosphonates reduced over time following initial prescription. For example, the overall mean persistence of oral bisphosphonates at 6 months, 1 year and 2 years post-index ranged from 34.8% to 71.3%, 17.6% to 74.8% and 12.9% to 60.6%, respectively. Dosing frequency appeared to affect persistence, with 6 month persistence of oral bisphosphonates with daily, weekly and monthly medication ranging between 27% and 45.5%, 45.7% and 72% and 56.8% and 56.8%, respectively. The findings of this current review were similar to that reported by Cramer et al who found 1 year persistence to bisphosphonate therapy ranged between 17.9% to 78.0%.[16] The review by Cramer and colleagues also reported that patients prescribed weekly oral bisphosphonates exhibited better persistence than those prescribed daily oral bisphosphonates (35.7% to 69.7% vs 26.1% to 55.7%).

High adherence rates of oral bisphosphonates may also lead to the most effective way of improving the benefit of these medications. For example, evidence suggests that the 2 year probability of fracture in females with osteoporosis may only begin to decrease as MPR exceeds 50%, and notably so after it exceeds 75%.[93] Across all included studies that reported MPR at 6 and 12 months, the proportion of patients adherent to medication varied from 31.7% to 72.0% and 55.6% to 90.0%, respectively. Mean medication possession ratio ranged from 0.59 to 0.81 (weekly) and 0.46 to 0.64 (daily), which are similar to the findings of a previous systematic review.[16]

Poor persistence and adherence to oral bisphosphonates, particularly in chronic asymptomatic disease such as osteoporosis, may compromise the clinical and economic effects of this class of medications among patients. In this review, 32 studies reported ≥50% persistence and adherence of alendronate, risedronate, etidronate and clodronate.[23 25 26 34–37 39 41 42 46 51 53 60 61 66 67 71 76 78 81–84 87 92 94 95 98 104 106 108] The remaining 57 studies reported ≤50% of persistence or adherence. The variation of patient persistence and adherence to medication across studies may be due to a number of factors and the healthcare system of the countries included within this review. Age[27 36 38 40 42 46–49 51 53 61 63 69 70 73 76 77 80 81 87 89 91 93 94 99 102 104 107] and medication dosing and frequency[22 24 31 38–43 45 46 49 51–54 63 64 78 80 81 83 86 91 92 97 99 100 102 103 107 108] as a determinant factor of osteoporosis was reported by 29 and 32 studies, respectively. The studies included also indicated that older patients were more likely to achieve higher persistence and adherence to oral bisphosphonates and that daily users of oral bisphosphonates medications have lower persistence and adherence than weekly users. Strengths and limitations to this review are acknowledged by the authors. This review involved a systematic and rigorous search for studies relating to patient persistence and adherence using real-world data. Measuring adherence and persistence based on real-world data is beneficial as it captures the timelines and frequency of refilling and thus measures the continuity of medication use.[110] Database-derived persistence and adherence assessment carries the advantage of being objective, quantifiable and simple.[111] Despite these strengths, it is also important to consider the following limitations. First, the calculation of persistence and adherence across the studies was heterogeneous. As a result, it was not possible to inferentially compare these studies with each other. Second, the calculation of persistence and adherence provided in the studies may not be true values. For example, billing and coding errors may occur because data for these studies were obtained from patients in unrestricted 'real world clinical settings' primarily for administrative purposes.[16] Collection and refilling of medication by patients does not guarantee that this medication was taken as directed, or at all. Third, although there are data for persistence and adherence of oral bisphosphonates from studies carried out from different geographical locations, it was not possible to identify any trends between the data and countries. Fourth, it is very difficult to capture the specific reasons for treatment discontinuation from prescription-driven or medical claim data rather than patient-derived data. The current review excluded data from randomised controlled trials to better reflect patient behaviour in the general osteoporosis population in real-life clinical practice. However, the exclusion of alternative designs such as open-label extension studies may infer an element of publication bias.

Additional studies are required to examine patient persistence or adherence in osteoporosis, including synthesis of qualitative studies to examine the reasons for discontinuation and real-world studies to examine healthcare resource use associated with osteoporosis

medication in relation to adherence and persistence. As osteoporosis is a chronic disease, clinicians should not only take into consideration the efficacy and side effects of medications when deciding on treatment options, but also ensure that realistic patient expectations from treatment are set through patient education and counselling. The patient's lifestyle should also be considered as this is likely to impact adherence and persistence with osteoporosis therapy.

CONCLUSIONS

This review has summarised patient persistence and adherence to oral bisphosphonates from a quality assessed studies that have used real-world data. The findings of this review suggest that real-world patient persistence and adherence with oral bisphosphonates medications is often poor and drops notably over time following the initial prescription of oral medications. However, adherence and persistence tended to be better in older patients and in patients who were prescribed weekly, rather than daily medications. To maximise adherence and persistence to oral bisphosphonates, it is important to consider their possible determinants including medication type and frequency, hospitalisation, age, history of fractures, race/ethnicity, gender, educational status and income as this may help to improve the health outcomes of patients with osteoporosis.

REFERENCES

1. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81:646–56.
2. Ross PD. Osteoporosis. Frequency, consequences, and risk factors. *Arch Intern Med* 1996;156:1399–411.
3. Olszynski WP, Shawn Davison K, Adachi JD, *et al*. Osteoporosis in men: epidemiology, diagnosis, prevention, and treatment. *Clin Ther* 2004;26:15–28.
4. Sinaki M. Postural Changes in Osteoporosis: Musculoskeletal Consequences. *Non-pharmacological management of osteoporosis*: Springer, Cham, 2017:207–17.
5. Orsini LS, Rousculp MD, Long SR, *et al*. Health care utilization and expenditures in the United States: a study of osteoporosis-related fractures. *Osteoporos Int* 2005;16:359–71.
6. Keen RW. Burden of osteoporosis and fractures. *Curr Osteoporos Rep* 2003;1:66–70.
7. Burge R, Dawson-Hughes B, Solomon DH, *et al*. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res* 2007;22:465–75.
8. Lewiecki EM. Bisphosphonates for the treatment of osteoporosis: insights for clinicians. *Ther Adv Chronic Dis* 2010;1:115–28.
9. Ammann P, Rizzoli R. Bone strength and its determinants. *Osteoporosis International* 2003;14:13–18.
10. MacLean C, Newberry S, Maglione M, *et al*. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med* 2008;148:197–213.
11. Iki M. [Primary, secondary and tertiary prevention of osteoporosis]. *Clin Calcium* 2006;16:1438–43.
12. Imaz I, Zegarra P, González-Enríquez J, *et al*. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. *Osteoporos Int* 2010;21:1943–51.
13. Diab DL, Watts NB. Bisphosphonates in the treatment of osteoporosis. *Endocrinol Metab Clin North Am* 2012;41:487–506.
14. Network for Excellence in Health Innovation. Network for excellence in health innovation (2015) Real world evidence: a new era for health care. innovation.http://www.nehi.net/writable/publication_files/file/rwe_issue_ brief_final.pdf
15. Burrell A, Wong P, Ollendorf D, *et al*. PHP46 Defining compliance/adherence and persistence: ispor special interest working group. *Value in Health* 2005;8:A194–5.
16. Cramer JA, Gold DT, Silverman SL, *et al*. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporosis International* 2007;18:1023–31.
17. Kothawala P, Badamgarav E, Ryu S, *et al*; *Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis*. Elsevier: Mayo Clinic Proceedings, 2007:1493–501.
18. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
19. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
20. Blouin J, Dragomir A, Fredette M, *et al*. Comparison of direct health care costs related to the pharmacological treatment of osteoporosis and to the management of osteoporotic fractures among compliant and noncompliant users of alendronate and risedronate: a population-based study. *Osteoporos Int* 2009;20:1571–81.
21. Cadarette SM, Solomon DH, Katz JN, *et al*. Adherence to osteoporosis drugs and fracture prevention: no evidence of healthy adherer bias in a frail cohort of seniors. *Osteoporos Int* 2011;22:943–54.
22. Carbonell-Abella C, Pages-Castella A, Javaid MK, *et al*. Early (1-year) discontinuation of different anti-osteoporosis medications compared: a population-based cohort study. *Calcif Tissue Int* 2015;97:535–41.
23. Cheng TT, Yu SF, Hsu CY, *et al*. Differences in adherence to osteoporosis regimens: a 2-year analysis of a population treated under specific guidelines. *Clin Ther* 2013;35:1005–15.
24. Downey TW, Foltz SH, Boccuzzi SJ, *et al*. Adherence and persistence associated with the pharmacologic treatment of osteoporosis in a managed care setting. *South Med J* 2006;99:570–5.
25. Hadji P, Klein S, Häussler B, *et al*. The bone evaluation study (BEST): patient care and persistence to treatment of osteoporosis in Germany. *Int J Clin Pharmacol Ther* 2013;51:868–72.
26. Halpern R, Becker L, Iqbal SU, *et al*. The association of adherence to osteoporosis therapies with fracture, all-cause medical costs, and all-cause hospitalizations: a retrospective claims analysis of female health plan enrollees with osteoporosis. *J Manag Care Pharm* 2011;17:25–39.
27. Hansen C, Pedersen BD, Konradsen H, *et al*. Anti-osteoporotic therapy in Denmark--predictors and demographics of poor refill compliance and poor persistence. *Osteoporos Int* 2013;24:2079–97.
28. Iolascon G, Gimigliano F, Orlando V, *et al*. Osteoporosis drugs in real-world clinical practice: an analysis of persistence. *Aging Clin Exp Res* 2013;25:137–41.
29. Abrahamsen B. Are long-term bisphosphonate users a reality? Dose years for current bisphosphonate users assessed using the danish national prescription database. *Osteoporos Int* 2013;24:369–72.
30. Blouin J, Dragomir A, Ste-Marie LG, *et al*. Discontinuation of antiresorptive therapies: a comparison between 1998-2001 and 2002-2004 among osteoporotic women. *J Clin Endocrinol Metab* 2007;92:887–94.
31. Brankin E, Walker M, Lynch N, *et al*. The impact of dosing frequency on compliance and persistence with bisphosphonates among postmenopausal women in the UK: evidence from three databases. *Curr Med Res Opin* 2006;22:1249–56.

32. Briesacher BA, Andrade SE, Yood RA, *et al*. Consequences of poor compliance with bisphosphonates. *Bone* 2007;41:882–7.
33. Briesacher BA, Andrade SE, Harrold LR, *et al*. Adoption of once-monthly oral bisphosphonates and the impact on adherence. *Am J Med* 2010;123:275–80.
34. Burden AM, Paterson JM, Solomon DH, *et al*. Bisphosphonate prescribing, persistence and cumulative exposure in Ontario, Canada. *Osteoporos Int* 2012;23:1075–82.
35. Burden AM, Paterson JM, Gruneir A, *et al*. Adherence to osteoporosis pharmacotherapy is underestimated using days supply values in electronic pharmacy claims data. *Pharmacoepidemiol Drug Saf* 2015;24:67–74.
36. Cheen MH, Kong MC, Zhang RF, *et al*. Adherence to osteoporosis medications amongst Singaporean patients. *Osteoporos Int* 2012;23:1053–60.
37. Colombo GL, Montecucco CM. 'Generic vs brand originator alendronate: analysis of persistence and compliance in five Local Healthcare Units in the Lombardy Region of Italy.' Clinical cases in mineral and bone metabolism. *The Official Journal Of The Italian Society Of Osteoporosis, Mineral Metabolism, And Skeletal Diseases,* 2013;10:195.
38. Copher R, Buzinec P, Zarotsky V, *et al*. Physician perception of patient adherence compared to patient adherence of osteoporosis medications from pharmacy claims. *Curr Med Res Opin* 2010;26:777–85.
39. Cotté FE, Fardellone P, Mercier F, *et al*. Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. *Osteoporos Int* 2010;21:145–55.
40. Cramer JA, Amonkar MM, Hebborn A, *et al*. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Curr Med Res Opin* 2005;21:1453–60.
41. Cramer JA, Lynch NO, Gaudin AF, *et al*. The effect of dosing frequency on compliance and persistence with bisphosphonate therapy in postmenopausal women: a comparison of studies in the United States, the United Kingdom, and France. *Clin Ther* 2006;28:1686–94.
42. Curtis JR, Westfall AO, Allison JJ, *et al*. Channeling and adherence with alendronate and risedronate among chronic glucocorticoid users. *Osteoporos Int* 2006;17:1268–74.
43. Curtis JR, Westfall AO, Cheng H, *et al*. Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday. *Osteoporos Int* 2008;19:1613–20.
44. Curtis JR, Westfall AO, Cheng H, *et al*. Benefit of adherence with bisphosphonates depends on age and fracture type: results from an analysis of 101,038 new bisphosphonate users. *J Bone Miner Res* 2008;23:1435–41.
45. Curtis JR, Xi J, Westfall AO, *et al*. Improving the prediction of medication compliance: the example of bisphosphonates for osteoporosis. *Med Care* 2009;47:334–41.
46. Devine J, Trice S, Finney Z, *et al*. A retrospective analysis of extended-interval dosing and the impact on bisphosphonate compliance in the US Military Health System. *Osteoporos Int* 2012;23:1415–24.
47. Devold HM, Furu K, Skurtveit S, *et al*. Influence of socioeconomic factors on the adherence of alendronate treatment in incident users in Norway. *Pharmacoepidemiol Drug Saf* 2012;21:297–304.
48. Dugard MN, Jones TJ, Davie MW. Uptake of treatment for osteoporosis and compliance after bone density measurement in the community. *J Epidemiol Community Health* 2010;64:518–22.
49. Ettinger MP, Gallagher R, MacCosbe PE. Medication persistence with weekly versus daily doses of orally administered bisphosphonates. *Endocr Pract* 2006;12:522–8.
50. Feldstein AC, Weycker D, Nichols GA, *et al*. Effectiveness of bisphosphonate therapy in a community setting. *Bone* 2009;44:153–9.
51. Gallagher AM, Rietbrock S, Olson M, *et al*. Fracture outcomes related to persistence and compliance with oral bisphosphonates. *J Bone Miner Res* 2008;23:1569–75.
52. Gold DT, Safi W, Trinh H. Patient preference and adherence: comparative US studies between two bisphosphonates, weekly risedronate and monthly ibandronate. *Curr Med Res Opin* 2006;22:2383–91.
53. Gold DT, Martin BC, Frytak JR, *et al*. A claims database analysis of persistence with alendronate therapy and fracture risk in post-menopausal women with osteoporosis. *Curr Med Res Opin* 2007;23:585–94.
54. Gold DT, Trinh H, Safi W. Weekly versus monthly drug regimens: 1-year compliance and persistence with bisphosphonate therapy. *Curr Med Res Opin* 2009;25:1831–9.
55. Hadji P, Claus V, Ziller V, *et al*. GRAND: the German retrospective cohort analysis on compliance and persistence and the associated risk of fractures in osteoporotic women treated with oral bisphosphonates. *Osteoporos Int* 2012;23:223–31.
56. Hadji P, Ziller V, Kyvernitakis J, *et al*. Persistence with bisphosphonates in patients with metastatic breast cancer: a retrospective database analysis. *J Cancer Res Clin Oncol* 2013;139:1149–55.
57. Hansen KE, Swenson ED, Baltz B, *et al*. Adherence to alendronate in male veterans. *Osteoporos Int* 2008;19:349–56.
58. Hawley S, Javaid MK, Rubin KH, *et al*. Incidence and predictors of multiple fractures despite high adherence to oral bisphosphonates: a binational population-based cohort study. *J Bone Miner Res* 2016;31:234–44.
59. Höer A, Seidlitz C, Gothe H, *et al*. 'Influence on persistence and adherence with oral bisphosphonates on fracture rates in osteoporosis.'. *Patient Preference and Adherence* 2009;3:25–30.
60. Ideguchi H, Ohno S, Hattori H, *et al*. Persistence with bisphosphonate therapy including treatment courses with multiple sequential bisphosphonates in the real world. *Osteoporos Int* 2007;18:1421–7.
61. Jones TJ, Petrella RJ, Crilly R. 'Determinants of persistence with weekly bisphosphonates in patients with osteoporosis.'. *The Journal Of Rheumatology* 2008;35:1865–73.
62. Kamatari M, Koto S, Ozawa N, *et al*. Factors affecting long-term compliance of osteoporotic patients with bisphosphonate treatment and QOL assessment in actual practice: alendronate and risedronate. *J Bone Miner Metab* 2007;25:302–9.
63. Kertes J, Dushenat M, Vesterman JL, *et al*. Factors contributing to compliance with osteoporosis medication. *Isr Med Assoc J* 2008;10:207–13.
64. Kishimoto H, Maehara M. Compliance and persistence with daily, weekly, and monthly bisphosphonates for osteoporosis in Japan: analysis of data from the CISA. *Arch Osteoporos* 2015;10:231.
65. Lakatos P, Takács I, Marton I, *et al*. A retrospective longitudinal database study of persistence and compliance with treatment of osteoporosis in hungary. *Calcif Tissue Int* 2016;98:215–25.
66. Landfeldt E, Ström O, Robbins S, *et al*. Adherence to treatment of primary osteoporosis and its association to fractures--the Swedish Adherence Register Analysis (SARA). *Osteoporos Int* 2012;23:433–43.
67. LeBlanc ES, Rosales AG, Balasubramanian A, *et al*. Risk factors for fracture among current, persistent users of bisphosphonates. *Osteoporos Int* 2015;26:713–25.
68. Li L, Roddam A, Gitlin M, *et al*. Persistence with osteoporosis medications among postmenopausal women in the UK General Practice Research Database. *Menopause* 2012;19:33–40.
69. Lin TC, Yang CY, Yang YH, *et al*. Alendronate adherence and its impact on hip-fracture risk in patients with established osteoporosis in Taiwan. *Clin Pharmacol Ther* 2011;90:109–16.
70. Lo JC, Pressman AR, Omar MA, *et al*. Persistence with weekly alendronate therapy among postmenopausal women. *Osteoporos Int* 2006;17:922–8.
71. Martin KE, Yu J, Campbell HE, *et al*. Analysis of the comparative effectiveness of 3 oral bisphosphonates in a large managed care organization: adherence, fracture rates, and all-cause cost. *J Manag Care Pharm* 2011;17:596–609.
72. McCombs JS, Thiebaud P, McLaughlin-Miley C, *et al*. Compliance with drug therapies for the treatment and prevention of osteoporosis. *Maturitas* 2004;48:271–87.
73. Modi A, Tang J, Sen S, *et al*. Osteoporotic fracture rate among women with at least 1 year of adherence to osteoporosis treatment. *Curr Med Res Opin* 2015;31:767–77.
74. Modi A, Siris S, Yang X, *et al*. Association between gastrointestinal events and persistence with osteoporosis therapy: analysis of administrative claims of a U.S. managed care population. *J Manag Care Spec Pharm* 2015;21:499–506.
75. Modi A, Sajjan S, Michael Lewiecki E, *et al*. Relationship between gastrointestinal events and compliance with osteoporosis therapy: an administrative claims analysis of the US managed care population. *Clin Ther* 2016;38:1074–80.
76. Netelenbos JC, Geusens PP, Ypma G, *et al*. Adherence and profile of non-persistence in patients treated for osteoporosis--a large-scale, long-term retrospective study in The Netherlands. *Osteoporos Int* 2011;22:1537–46.
77. Olsen KR, Hansen C, Abrahamsen B. Association between refill compliance to oral bisphosphonate treatment, incident fractures, and health care costs--an analysis using national health databases. *Osteoporos Int* 2013;24:2639–47.
78. Papaioannou A, Ioannidis G, Adachi JD, *et al*. Adherence to bisphosphonates and hormone replacement therapy in a tertiary

care setting of patients in the CANDOO database. *Osteoporos Int* 2003;14:808–13.

79. Patrick AR, Brookhart MA, Losina E, *et al*. The complex relation between bisphosphonate adherence and fracture reduction. *J Clin Endocrinol Metab* 2010;95:3251–9.

80. Penning-van Beest FJ, Goettsch WG, Erkens JA, *et al*. Determinants of persistence with bisphosphonates: a study in women with postmenopausal osteoporosis. *Clin Ther* 2006;28:236–42.

81. Penning-van Beest FJ, Erkens JA, Olson M, *et al*. Loss of treatment benefit due to low compliance with bisphosphonate therapy. *Osteoporos Int* 2008;19:511–7.

82. Penning-van Beest FJ, Erkens JA, Olson M, *et al*. Determinants of non-compliance with bisphosphonates in women with postmenopausal osteoporosis. *Curr Med Res Opin* 2008;24:1337–44.

83. Rabenda V, Mertens R, Fabri V, *et al*. Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. *Osteoporos Int* 2008;19:811–8.

84. Recker RR, Gallagher R, MacCosbe PE. Effect of dosing frequency on bisphosphonate medication adherence in a large longitudinal cohort of women. *Mayo Clin Proc* 2005;80:856–61.

85. Reynolds K, Muntner P, Cheetham TC, *et al*. Primary non-adherence to bisphosphonates in an integrated healthcare setting. *Osteoporos Int* 2013;24:2509–17.

86. Richards JS, Cannon GW, Hayden CL, *et al*. Adherence with bisphosphonate therapy in US veterans with rheumatoid arthritis. *Arthritis Care Res* 2012;64:1864–70.

87. Rietbrock S, Olson M, van Staa TP. The potential effects on fracture outcomes of improvements in persistence and compliance with bisphosphonates. *QJM* 2009;102:35–42.

88. Roerholt C, Eiken P, Abrahamsen B. Initiation of anti-osteoporotic therapy in patients with recent fractures: a nationwide analysis of prescription rates and persistence. *Osteoporos Int* 2009;20:299–307.

89. Roughead EE, Ramsay E, Priess K, *et al*. Medication adherence, first episode duration, overall duration and time without therapy: the example of bisphosphonates. *Pharmacoepidemiol Drug Saf* 2009;18:69–75.

90. Sampalis JS, Adachi JD, Rampakakis E, *et al*. Long-term impact of adherence to oral bisphosphonates on osteoporotic fracture incidence. *J Bone Miner Res* 2012;27:202–10.

91. Scotti L, Arfè A, Zambon A, *et al*. Cost-effectiveness of enhancing adherence with oral bisphosphonates treatment in osteoporotic women: an empirical approach based on healthcare utilisation databases. *BMJ Open* 2014;4:e003758.

92. Sheehy O, Kindundu CM, Barbeau M, *et al*. Differences in persistence among different weekly oral bisphosphonate medications. *Osteoporos Int* 2009;20:1369–76.

93. Siris ES, Harris ST, Rosen CJ, *et al*. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clin Proc* 2006;81:1013–22.

94. Siris ES, Pasquale MK, Wang Y, *et al*. Estimating bisphosphonate use and fracture reduction among US women aged 45 years and older, 2001-2008. *Journal of Bone and Mineral Research* 2011;26:3–11.

95. Soong YK, Tsai KS, Huang HY, *et al*. Risk of refracture associated with compliance and persistence with bisphosphonate therapy in Taiwan. *Osteoporos Int* 2013;24:511–21.

96. Ström O, Landfeldt E. The association between automatic generic substitution and treatment persistence with oral bisphosphonates. *Osteoporos Int* 2012;23:2201–9.

97. Sunyecz JA, Mucha L, Baser O, *et al*. Impact of compliance and persistence with bisphosphonate therapy on health care costs and utilization. *Osteoporos Int* 2008;19:1421–9.

98. Tafaro L, Nati G, Leoni E, *et al*. Adherence to anti-osteoporotic therapies: role and determinants of "spot therapy". *Osteoporos Int* 2013;24:2319–23.

99. van Boven JF, de Boer PT, Postma MJ, *et al*. Persistence with osteoporosis medication among newly-treated osteoporotic patients. *J Bone Miner Metab* 2013;31:562–70.

100. van den Boogaard CH, Breekveldt-Postma NS, Borggreve SE, *et al*. Persistent bisphosphonate use and the risk of osteoporotic fractures in clinical practice: a database analysis study. *Curr Med Res Opin* 2006;22:1757–64.

101. Wang Z, Ward MM, Chan L, *et al*. Adherence to oral bisphosphonates and the risk of subtrochanteric and femoral shaft fractures among female medicare beneficiaries. *Osteoporos Int* 2014;25:2109–16.

102. Weiss TW, Henderson SC, McHorney CA, *et al*. Persistence across weekly and monthly bisphosphonates: analysis of US retail pharmacy prescription refills. *Curr Med Res Opin* 2007;23:2193–203.

103. Weycker D, Macarios D, Edelsberg J, *et al*. Compliance with drug therapy for postmenopausal osteoporosis. *Osteoporos Int* 2006;17:1645–52.

104. Weycker D, Lamerato L, Schooley S, *et al*. Adherence with bisphosphonate therapy and change in bone mineral density among women with osteoporosis or osteopenia in clinical practice. *Osteoporos Int* 2013;24:1483–9.

105. Yeaw J, Benner JS, Walt JG, *et al*. Comparing adherence and persistence across 6 chronic medication classes. *J Manag Care Pharm* 2009;15:728–40.

106. Yood RA, Emani S, Reed JI, *et al*. Compliance with pharmacologic therapy for osteoporosis. *Osteoporos Int* 2003;14:965–8.

107. Zambon A, Baio G, Mazzaglia G, *et al*. Discontinuity and failures of therapy with bisphosphonates: joint assessment of predictors with multi-state models. *Pharmacoepidemiol Drug Saf* 2008;17:260–9.

108. Ziller V, Kostev K, Kyvernitakis I, *et al*. Persistence and compliance of medications used in the treatment of osteoporosis--analysis using a large scale, representative, longitudinal German database. *Int J Clin Pharmacol Ther* 2012;50:315–22.

109. Hess LM, Raebel MA, Conner DA, *et al*. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother* 2006;40:1280–8.

110. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. *Am J Manag Care* 2005;11:449–57.

111. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997;50:105–16.