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

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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

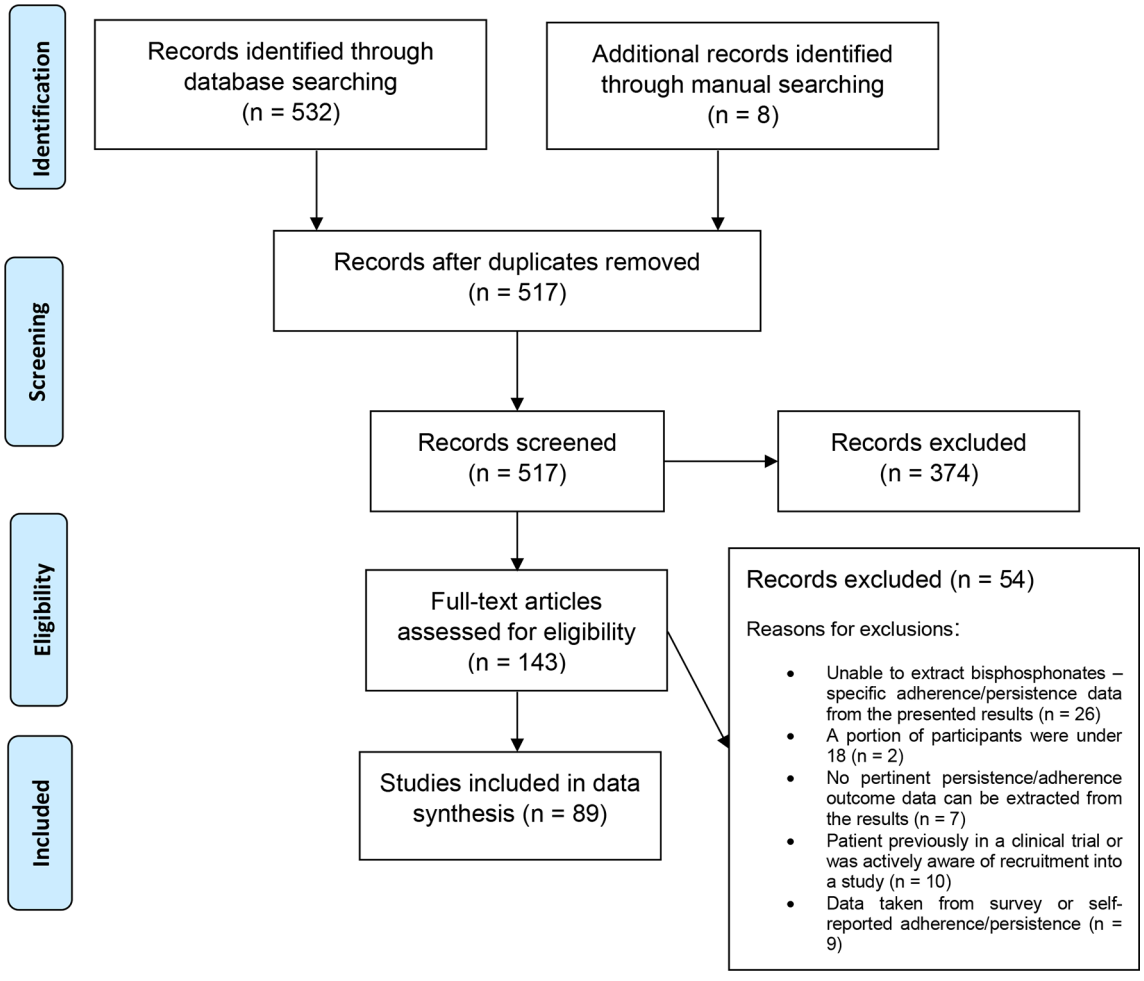

Figure 1 The preferred reporting for systematic reviews and meta-analyses diagram representing the systematic literature search.[94]

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	2002to 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	15 330 (71.7)	233	n/a	55% (weekly regimen), 42.8% (daily regimen)	n/a
Burden *et al*[34]	Alendronate, etidronate, risedronate	451 113 (75.6)	n/a	n/a	63.10%	46.40%
Burden *et al*[35]	Alendronate, etidronate, risedronate	337 329 (75.7)	n/a	n/a	56%*, 66%†	n/a
Carbonell-Abella *et al*[22]	Alendronate, ibandronate, risedronate	118 829 (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	22 363 (n/a)	189.8* (weekly), 196.3* (monthly)	n/a	n/a	n/a
Downey *et al*[24]	Alendronate, risedronate	10 566 (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	211 319 (n/a)	n/a	n/a	56.7%* (weekly), 39%* (daily)	n/a
Gallagher *et al*[51]	Alendronate, risedronate	44 531 (n/a)	n/a	n/a	58.3%§	n/a
Gold *et al*[52]	Ibandronate, risedronate	234 862 (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	263 383 (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	19 752 (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 (70.4)	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
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[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

Table 2 Continued

Reference	Medications	Population (mean age)	Length of persistence (days)	Patient persistence		
				6 months	1 year	2 years
Ziller *et al*[108]	Alendronate, etidronate, risedronate	268 568 (63.3)	239.8 hour (alendronate 70 mg), 218.7§ (alendronate +vitamin D), 246.4§ (etidronate), 256.4§ (ibandronate 150 mg), 190.9§ (risedronate)	n/a	44.8% hour (alendronate 70 mg), 37.8%h (alendronate +vitamin D), 43.4%h (etidronate), 50.8%h (ibandronate), 30.3%h (risedronate)	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 x prescription length, n/a means not reported.

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 over-time 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 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.

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