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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

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.

INTRODUCTION

Osteoporosis is a chronic global health condition, characterised by low bone density and bone structure deterioration. About a third of men and more than half of all women experience osteoporosis during their lives. Moreover, evidence suggests that fracture-related mortality rate is higher in men than women. 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. 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. 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 ($6,746). The total cost estimates for the treatment of osteoporosis and subsequent care in the USA was around $7 billion in 2003 and this is expected to increase by...
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. Bisphosphonate treatments such as etidronate, alendronate, ibandronate, risedronate and zoledronic acid are able to prevent vertebral fractures more than placebo. 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. 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. 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 use of PROSPERO, with registration number CRD: 42017059894.

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. 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 adhers* OR non-adhers* OR complian* OR discontinu* OR prescri* OR pattern* OR gap* (TITLE) AND Osteopor* OR Osteopen* OR (Bone AND loss) OR Alendron* OR Etidron* OR Ibandron* OR Risedron* OR Biphosphonat* (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. 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

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

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## 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 et al     | National prescription                                      | Denmark                  | 1995 to 2007                  | 10 years            | 6/6                 |
| Blouin et al         | Régie de l’assurance maladie du Québec                     | Canada                   | 2002 to 2004                  | 2 years             | 8/8                 |
| Blouin et al         | Régie de l’assurance maladie du Québec                     | Canada                   | 1998 to 2001 & 2000 to 2004   | 1 year              | 6/6                 |
| Brankin et al        | General practice research database IMS disease analyser    | UK                       | 2001 to 2004                  | 1 year              | 6/6                 |
|                      | Doctors independent network database                      |                          |                               |                     |                     |
| Briesacher et al     | MarketScan research databases                              | USA                      | 2000 to 2004                  | 1 to 3 years        | 6/6                 |
| Briesacher et al     | MarketScan commercial claims and encounters and Medicare   | N/A                      | 2001 to 2006                  | 1 year              | 6/6                 |
| Burden et al         | Ontario drug benefit database                              | Canada                   | 1996 to 2009                  | 1 to 9 years        | 6/6                 |
| Burden et al         | Ontario drug benefit database                              | Canada                   | 2001 to 2012                  | 1 year              | 6/6                 |
| Cadarette et al      | Pennsylvania pharmaceutical assistance contract            | USA                      | 1995 to 2005                  | 6 months            | 6/6                 |
| Carbonell-Abella et al | Sistema d’informacio per al desenvolupament de la investigacio en atencio primaria | Spain                    | 2007 to 2010                  | 1 year              | 8/8                 |
| Cheen et al          | CITRIX patient record management system and MAXCARE prescription record system, Singapore General Hospital | Singapore                | 2007 to 2008                  | 2 years             | 6/6                 |
| Cheng et al          | Chang-Gung Memorial Hospital, Kaohsiung Medical Centre     | Taiwan                   | 2001 to 2007                  | 2 years             | 8/8                 |
| Colombo and Montecucco | Aziende sanitarie locali                        | Italy                    | 2008 to 2008                  | 34 months           | 6/6                 |
| Copher et al         | Administrative claims                                      | USA                      | 2002 to 2006                  | 1 year              | 8/8                 |
| Cotté et al          | Thales longitudinal prescription                           | France                   | 2007 to 2008                  | 1 year              | 8/8                 |
| Cramer et al         | De-identified healthcare claims                             | USA                      | 1997 to 2002                  | 1 year              | 8/8                 |
| Cramer et al         | 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         | Linked enrolment, outpatient encounter, pharmacy and procedural billing | USA                      | 2001 to 2004                  | 39 months           |                     |
| Curtis et al         | Unidentified administrative claims                          | USA                      | 1998 to 2005                  | 3 years             | 6/6                 |
| Curtis et al         | Unidentified administrative claims                          | USA                      | 1998 to 2005                  | 3 years             | 6/6                 |
| Curtis et al         | Unidentified administrative claims                          | USA                      | 1998 to 2005                  | 1 year              | 6/6                 |
| Devine et al         | Pharmacy data transaction service data warehouse           | USA                      | 2006 to 2008                  | 1 year              | 8/8                 |
| Reference       | Type of database                                 | Country            | Time frame of data collection | Length of follow-up | Adjusted NOS scores |
|-----------------|--------------------------------------------------|--------------------|------------------------------|---------------------|---------------------|
| Devold et al    | Norwegian prescription database                  | Norway             | 2005 to 2009                 | 5 years             | 8/8                 |
| Downey et al    | National administrative claims                   | USA                | 2001 to 2003                 | 1 year              | 6/6                 |
| Dugard et al    | An unidentified database of GP records           | UK                 | 1996 to 2002                 | 5 years             | 6/6                 |
| Ettinger et al  | A large database was accessed through             | USA                | 2002 to 2003                 | 1 year              | 6/6                 |
| Feldstein et al | Undefined health maintenance organisation        | USA                | 1996 to 2006                 | 2.7 years           | 6/6                 |
| Gallagher et al | General practice research database               | UK                 | 1987 to 2006                 | 2.3 years           | 8/8                 |
| Gold et al      | IMS longitudinal prescription                     | USA                | X to 2005                    | 6 months            | 8/8                 |
| Gold et al      | Unidentified pharmacy prescription                | USA                | 1996 to 2003                 | 2 years             | 6/6                 |
| Gold et al      | IMS longitudinal prescription                     | USA                | 1996 to 2003                 | 1 year              | 8/8                 |
| Hadji et al     | IMS disease analyser patient                     | Germany            | 2004 to 2007                 | 2 years             | 6/6                 |
| Hadji et al     | Techniker krankenkasse                           | Germany            | 2006 to 2009                 | 2 years             | 6/6                 |
| Hadji et al     | IMS disease analyser patient                     | Germany            | 2001 to 2010                 | 1 year              | 6/6                 |
| Halpern et al   | Unidentified administrative claims                | USA                | 2002 to 2006                 | 18 months           | 8/8                 |
| Hansen et al    | Danish national registers                        | Denmark            | 1996 to 2006                 | 5.2 years           | 6/6                 |
| Hansen et al    | Veteran affairs pharmacy service records          | USA                | 2000 to 2004                 | 2 years             | 8/8                 |
| Hawley et al    | Sistema d’informazione per al desenvolupament de l’investigació en atenció primària | Spain              | 2006 to 2007                 | 6 months            | 6/6                 |
| Hoer et al      | Claims database of a statutory sickness fund     | Germany            | 2000 to 2004                 | 2 years             | 6/6                 |
| Ideguchi et al  | Yokohama City University Medical Centre          | Japan              | 2000 to 2005                 | 5 years             | 6/6                 |
| Iolascon et al  | Unidentified administrative prescription database | Italy              | 2008 to 2010                 | 1 year              | 6/6                 |
| Jones et al     | Ontario Drugs Database and Brogan Inc. private payer database | Canada             | 2003 to 2006                 | 1 year              | 6/6                 |
| Kamatari et al  | Pharmacy prescription database                   | Japan              | 2000 to 2005                 | 4 years             | 6/6                 |
| Kertes et al    | Maccabi healthcare services database             | Israel             | 2003 to 2004                 | 1 year              | 6/6                 |
| Kishimoto and Machara | Platform for clinical information statistical analysis database | Japan              | 2006 to 2014                 | 8 years             | 6/6                 |
| Lakatos et al   | National health insurance fund administration    | Hungary            | 2004 to 2013                 | 2 years             | 6/6                 |
| Landfeldt et al | Swedish prescribed drug register                  | Sweden             | 2005 to 2009                 | 4 years             | 6/6                 |
| LeBlanc et al   | Kaiser Permanente Northwest                      | USA                | 1997 to 2011                 | 5 years             | 6/6                 |
| Li et al        | General practice research database               | UK                 | 1995 to 2008                 | 5 years             | 6/6                 |
| Lin et al       | Unidentified health insurance database           | Taiwan             | 2003 to 2006                 | 1 year              | 6/6                 |
| 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                              | USA                                    | 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                                      | 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 rheumatoid arthritis registry                       | 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                     | Canada                                 | 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
(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 56 59–68 70 78 80 83 87 90 92 95 99 100 103 105 108 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 56 58 61 65 68 74 76 78 83 92 99 100 103 105 108 and 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 years25 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 63 68 alendronate42 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

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**Table 1**

| Reference                  | Type of database                                      | Country                  | Time frame of data collection | Length of follow-up | Adjusted NOS scores |
|-----------------------------|-------------------------------------------------------|--------------------------|------------------------------|---------------------|---------------------|
| Soong et al96               | National health insurance research database           | Taiwan                   | 2004 to 2006                 | 1 year              | 6/6                 |
| Ström36                     | Swedish prescribed drug register                      | Sweden                   | 2005 to 2009                 | 4 years             | 6/6                 |
| Sunycz et al97              | Thomson healthcare, MarketScan, Medicare,            | USA                      | 2000 to 2002                 | 3 years             | 6/6                 |
| Tafaro et al98              | General practitioner databases                        | Italy                    | 2001 to 2007                 | 300 days            | 6/6                 |
| Van Boven et al99           | The InterAction database                              | Netherlands              | 2003 to 2011                 | 1 year              | 6/6                 |
| Van den Boogaard et al100   | PHARMO record linkage system                          | Netherlands              | 1996 to 2003                 | 3 years             | 6/6                 |
| Wang et al101               | Centres for Medicare and Medicaid services           | USA                      | 2006 to 2010                 | 5 years             | 6/6                 |
| Weiss et al102              | IMS longitudinal prescription database                 |                          | 2004 to 2006                 | 1 year              | 6/6                 |
| Weycker et al103            | PharMetrics patient-centric database                  | USA                      | 1998 to 2003                 | 5.5 years           | 6/6                 |
| Weycker et al104            | Health alliance plan of Henry Ford Health System     | USA                      | 2002 to 2007                 | 27.1 months         | 6/6                 |
| Yeaw et al105               | PharMetrics patient-centric database                  | USA                      | 2005 to 2005                 | 1 to 2 years        | 6/6                 |
| Yood et al106               | Unidentified health maintenance organisation          | USA                      | 1998 to 1999                 | 18 months           | 6/6                 |
| Zambon et al107             | Health services databases of Lombardy                | Italy                    | 2003 to 2005                 | 3 years             | 6/6                 |
| Ziller et al108             | 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.
Table 2  Persistence data for osteoporosis medications by study

| Reference         | Medications                  | Population (mean age) | Length of persistence (days) | Patient persistence |
|-------------------|------------------------------|-----------------------|------------------------------|---------------------|
| Brankin et al     | Alendronate, risedronate     | 15330 (71.7)          | 233                          | n/a                 |
| Burden et al      | Alendronate, etidronate, risedronate | 451113 (75.6)        | n/a                          | 63.10%              |
| Burden et al      | Alendronate, etidronate, risedronate | 337329 (75.7)        | n/a                          | 56%§, 66%†          |
| Carbonell-Abella  | Alendronate, ibandronate, risedronate | 118829 (66.9)        | n/a                          | 14.1% (ibandronate daily), 56.5% (alendronate weekly), 35.8% (ibandronate monthly), 7.7% (risedronate daily), 31.2% (risedronate weekly), 40.0% (risedronate monthly) |
| Cheen et al       | Alendronate, risedronate     | 798 (68.5)            | n/a                          | 69%*                |
| Cheng et al       | Alendronate                  | 1745 (68.1)           | n/a                          | 57.1%*              |
| Cotté et al       | Alendronate, risedronate     | 2990 (69.9)           | 169                          | 45.7%*              |
| Cramer et al      | Alendronate, risedronate, ibandronate | 2741 (n/a)          | 196                          | 44.6%* (daily), 58.1%* (weekly) |
| Cramer et al      | Alendronate, risedronate     | 2741 (73)             | 204                          | 50%‡ (weekly), 38.6%‡ (daily) |
| Curtis et al      | Alendronate, risedronate     | 1158 (53)             | n/a                          | 51.4%§ (alendronate), 46.8%§ (risedronate) |
| Devine et al      | Alendronate, ibandronate, risedronate | 22363 (n/a)          | 189.8* (weekly), 196.3* (monthly) | n/a                 |
| Downey et al      | Alendronate, risedronate     | 10566 (66.4)          | n/a                          | 21.3% (alendronate), 19.4% (risedronate) |
| Dugard et al      | Not stated                   | 254 (76.7)            | n/a                          | 74%¶                |
| Ettinger et al    | Alendronate, risedronate     | 211319 (n/a)          | n/a                          | 56.7%* (weekly), 39%* (daily) |
| Gallagher et al   | Alendronate, risedronate     | 44531 (n/a)           | n/a                          | 58.3%§               |
| Gold et al        | Ibandronate, risedronate     | 234862 (n/a)          | 144.3§ (ibandronate), 100.1§ (risedronate) | n/a                 |
| Gold et al        | Alendronate                  | 4769 (n/a)            | 261*                         | 38%* (daily), 49%* (weekly) |
| Gold et al        | Ibandronate, risedronate     | 263383 (66.21)        | 151.54§ (ibandronate) 250.04§ (risedronate) | n/a                 |
| Hadji et al       | Alendronate, clodronate, etidronate, risedronate | 4147 (n/a)          | 145.5*                       | 27.9%*               |
| Hadji et al       | Alendronate, clodronate, etidronate, risedronate | 19752 (n/a)          | n/a                          | 26%*                |

Continued
| Reference                | Medications                                      | Population (mean age) | Length of persistence (days) | Patient persistence |
|--------------------------|--------------------------------------------------|-----------------------|-----------------------------|---------------------|
|                          |                                                  |                       |                             | 6 months | 1 year | 2 years |
| Hadiji et al[26]         | Clodronate, ibandronate, pamidronate, zoledronate| 280 (63.2)            | n/a                         | n/a      | n/a    | 45.6%§  |
| Hansen et al[27]         | Alendronate, other oral bisphosphonates          | 100556 (70.4)         | 1463** (alendronate) 532.9** (clodronate) 963.6** (etidronate) 1408.9** (ibandronate) 1018** (risedronate) | n/a      | n/a    | n/a     |
| Hansen et al[27]         | Alendronate                                      | 198 (71)              | n/a                         | n/a      | n/a    | 28%     |
| Hawley et al[28]         | Not stated                                       | 21385 (n/a)           | n/a                         | 45.65%   | n/a    | n/a     |
| Hoer et al[28]           | Alendronate, etidronate, risedronate             | 4451 (n/a)            | n/a                         | 71.3%*   | 47.3%* | 14.5%*  |
| Ideguchi et al[30]       | Alendronate, etidronate, risedronate             | 1307 (61.3)           | n/a                         | 74.8%§   | n/a    | 60.6%§  |
| Iolascon et al[28]       | Alendronate, risedronate, ibandronate            | 18515 (68.9)          | n/a                         | 12.6%* (alendronate), 15.8%* (risedronate), 21.6%* (ibandronate) | n/a     |
| Jones et al[31]          | Alendronate, risedronate, etidronate             | 62897 (n/a)           | n/a                         | 72%* (alendronate weekly), 71.2%* (risedronate weekly), 56.3%* (alendronate weekly), 54.4%* (risedronate weekly) | n/a     |
| Kamatari et al[32]       | Alendronate, risedronate                         | 1274 (74)             | n/a                         | 42.5%* (alendronate), 44.6%* (risedronate) | n/a     |
| Kertes et al[33]         | Alendronate, risedronate                         | 4448 (n/a)            | 216*                        | n/a      | n/a    | 46%*    |
| Kishimoto and Machara[34]| Not stated                                       | 12230 (59.8)          | n/a                         | 33.2%* (daily regimen) | 13.0%* (daily), 32.7%* (weekly regimen) | 50.4%* (weekly regimen) |
| Lakatos et al[35]        | Alendronate, risedronate, ibandronate            | 296300 (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[36]      | Alendronate, risedronate                         | 56586 (71)            | n/a                         | 55%†† (alendronate), 54%†† (risedronate) | 38%††† (alendronate), 38%††† (risedronate) | |
| LeBlanc et al[37]        | Not stated                                       | 14674 (71)            | n/a                         | 58%¶¶    | 23%‡‡  |         |
| Li et al[38]             | Alendronate, etidronate, risedronate, ibandronate| 66116 (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[39]             | Alendronate                                      | 13455 (68.8)          | 378†                        | 40%†     | 50%†   | n/a     |
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             | 75593 (64.4)          | 115.6*                      | 39.30%*  | n/a    | n/a     |
| Netelenbos et al[74]       | Alendronate, etidronate, ibandronate, risedronate| 105506 (69.2)         | n/a                         | 43.10%§§ | n/a    | n/a     |
| Papaioannou et al[78]      | Alendronate, etidronate                          | 1673 (66.8)           | 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                         | 42.9%*   | n/a    | n/a     |
| Rabenda et al[83]          | Alendronate                                      | 54807 (n/a)           | n/a                         | 58%¶¶    | 40%¶¶ | n/a     |
| Richards et al[86]         | Alendronate, risedronate                         | 573 (68.7)            | 1176§                       | n/a      | n/a    | n/a     |
| Retbrock et al[87]         | Alendronate, risedronate                         | 44531 (71)            | n/a                         | 58.30%   | n/a    | 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                                       | 42885 (80.8)          | n/a                         | n/a      | n/a    | n/a     |
| Sampalis et al[90]         | Alendronate, ibandronate, Risedronate            | 636114 (72)           | n/a                         | 41.0%*   | 41.0%* | 26.6%*  |
| Sheehy et al[92]           | Alendronate                                      | 32804 (n/a)           | n/a                         | 79%***   | 65%*** | n/a***  |
| Siris et al[93]            | Alendronate, risedronate                         | 35357 (65.3)          | n/a                         | n/a      | n/a    | 20%*    |
| Soong et al[95]            | Alendronate                                      | 32604 (72.4)          | n/a                         | 48.03%*  | 17.6%* | n/a     |
| Ström[96]                  | Alendronate, risedronate                         | 36433 (70.2)          | n/a                         | n/a      | 51.67%†† | n/a     |
| Sunyecz et al[97]          | Alendronate, risedronate                         | 32944 (64.3)          | n/a                         | n/a      | n/a    | 21%*3 years† |
| Van Boven et al[98]        | Alendronate, etidronate, ibandronate, risedronate| 8610 (67.5)           | n/a                         | 48.9%*   | n/a    | 40%*3 years† |
| Van den Boogaard et al[100]| Alendronate, etidronate, risedronate             | 14760 (n/a)           | n/a                         | 43.60%   | n/a    | 27.40%  |
| Weiss et al[102]           | Alendronate, ibandronate, risedronate            | 165955 (67.1)         | 109*                        | n/a      | n/a    | n/a     |
| Weycker et al[103]         | Alendronate, risedronate                         | 18822 (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, etidronate, pamidronate | 10268 (56.9)         | n/a                         | 56%*     | 41%†   | n/a     |
Out of 19 studies, 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.

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). Few studies reported MPR that ranged between 55.6% and 90% for 6-months follow-up (table 3). Across all studies that reported MPR at 1 year, the proportion of patients adherent to medication varied from 31.7% to 72.0%.

Across six studies adherence at 2 years was less than that of adherence at 1 year, ranging from 34.5% to 47.9%. Parallel to this, six studies reported the proportion of patients who achieved MPR ≥ 80% at 3 years varied between 23% and 47.9%. 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, prior bone mineral density (BMD) test, chronic disease score, hospitalisation, medication type and frequency, age, history of fractures, race/ethnicity and number of co-medication, glucocorticoid, gender, education status, income, marital status, history of

| Reference | Medications | Population (mean age) | Length of persistence (days) | Patient persistence | Adherence | Outcomes |
|-----------|-------------|-----------------------|-----------------------------|---------------------|-----------|----------|
| Ziller et al | Alendronate, etidronate, risedronate | 108 | 6 months: 208±56 (63.3) | n/a | n/a | n/a |
| | | | 1 year: 239.8±18.7 | n/a | n/a | n/a |
| | | | 2 years: 246.4±18.7 | n/a | n/a | n/a |

*Persistence with no refill gaps ≥ 30 days. †Persistence with no refill gaps > 60 days. +Persistence was defined as length of time until refill gap > 12 months. #Persistence was defined as length of time until refill gap > 6 months. Other outcomes: patient persistence defined as length of time until refill gap exceeding 1.5 x prescription length, n/a means not reported.
Table 3  Adherence data for osteoporosis medications

| Reference          | Medication                  | Population (mean age) | Compliance, mean MPR |
|--------------------|-----------------------------|-----------------------|----------------------|
| Abrahamsen et al   | Alendronate                 | 58674 (n/a)           | <5 years 5 to 10 years >10 years |
|                    | Alendronate (92%)           | Alendronate (84%)     | Alendronate (76%)    |
|                    | Etidronate (92%)            | Etidronate (89%)      | Etidronate (88%)     |
|                    | Ibandronate (81%)           | Ibandronate (75%)     | Ibandronate (70%)    |
|                    | Risedronate (91%)           | Risedronate (80%)     | Risedronate (75%)    |
| Blouin et al       | Alendronate                 | 15027 (76.6)          | 69.7%±34.8%          |
|                    | Risedronate                 |                       |                      |
| Briesacher et al   | Alendronate, risdonate      | 17988 (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   | Alendronate, ibandronate,  | 61125 (62.1)          | At 1 year (monthly medication), At 1 year (weekly medications) At 1 year (daily medication) |
|                    | risedronate                 |                       | 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%)       |
|                    | 14% (MPR <20%)              | 42% (MPR <20%)        |                      |
| Burden et al       | Alendronate, etidronate,    | 337329 (75.7)         | 70%*                 |
|                    | risedronate                 |                       |                      |
| Cadarette et al    | Alendronate, risedronate    | 20205 (79)            | 49.8% (PDC ≥80%); 14.5% (PDC 51% to 79%); 35.7% (PDC <50%) |
| Cheen et al        | Alendronate, risedronate    | 798 (68.5)            | 78.90%               |
| Cheng et al        | Alendronate                 | 1745 (68.1)           | At 1 year; 61.9%     |
|                    | 70%*                        | (MPR >80%)            | At 2 years, 47.9%    |
| Colombo and        | Generic alendronate,        | 20711 (73)            | 69% to 74%           |
| Montecucco         | branded alendronate         |                       |                      |
| Copher et al       | Alendronate, ibandronate,   | 1587 (62.3)           | 48.70% (95% CI 46.2 to 51.2) |
|                    | risedronate                 |                       |                      |
| Cotté et al        | 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       | Alendronate, risedronate,   | 2741 (n/a)            | 60.60%               |
|                    | ibandronate                 |                       |                      |
| Cramer et al       | Alendronate, risedronate    | 2741(73)              | 64%                  |
| Curtis et al       | Alendronate, risedronate    | 1158 (53)             | 73%                  |
| Curtis et al       | Alendronate, risedronate    | 25446 (n/a)           | At 2 years, 29.4%    |
|                    | Achieved MPR >80% = 27.2%   |                      | At 3 years,          |
|                    | Achieved MPR >80% = 29.4%   |                      |                      |

Continued
Table 3  Continued

| Reference          | Medication                             | Population (mean age) | Compliance, mean MPR |
|--------------------|----------------------------------------|-----------------------|----------------------|
| Curtis et al\(^65\) | Alendronate                            | 101 038 (n/a)         | Achieving MPR >80% = 44% |
|                    |                                        |                       | Achieved MPR <50% = 34.9% |
|                    | Ibandronate, risedronate               |                       |                      |
| Devine et al\(^66\) | 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% |
| Feldstein et al\(^60\) | Alendronate, ibandronate, risedronate | 1829 (72)            | Achieving MPR >80% = 44% |
|                    |                                        |                       | Achieving MPR >80% = 42% |
| 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\(^65\) | Alendronate, clodronate, etidronate, risedronate | 4147 (n/a)           | Achieving MPR >80% = 66.3% |
|                    |                                        |                       | Achieving MPR <80% = 22.7% |
| Halpern et al\(^78\) | 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\(^77\) | Alendronate                            | 198 (71)              | At 12 months,       |
|                    |                                        |                       | At 2 years,         |
|                    |                                        |                       | Achieving MPR >80% = 59% |
|                    |                                        |                       | Achieving MPR >80% = 54% |
| Hoer et al\(^69\)  | 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\(^74\) | 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\(^85\)   | Alendronate                           | 89 363 (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% (risedronate)   |
|                    |                                        |                       | 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
upper gastrointestinal problems, tobacco use, rheumatoid arthritis, national insurance, hormone replacement therapy, clinical service use, mental disorder, diabetes and co-payments were mentioned as determinants of persistence and adherence. The relationship of these determinants to patients’ persistence and adherence to medication is described below.

### Table 3

| Reference            | Medication                          | Population (mean age) | Compliance, mean MPR |
|----------------------|-------------------------------------|-----------------------|-----------------------|
| Olsen et al          | 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 | Alendronate, risedronate            | 8822 (69.4)           | At 3 months, achieving MPR ≥80% = 28.4% |
|                      |                                     |                       | Daily = 60.3% Achieving MPR ≥80%, Weekly = 60.3% |
|                      |                                     |                       | Daily = 72.8% Achieving MPR ≥80%, Weekly = 72.8% |
|                      |                                     |                       | Daily = 50.2% |
| Penning-van Beest et al | Alendronate, risedronate            | 8822 (n/a)            | Achieving MPR ≥80% = 58% |
| Rabenda et al        | Alendronate                         | 54,807 (n/a)          | 64.70% |
| Recker et al         | Alendronate, risedronate            | 211,319 (n/a)         | 54% (daily regimen) |
| Richards et al       | Alendronate, risedronate            | 573 (68.7)            | 69% |
| Sampalis et al       | Alendronate, ibandronate, risedronate | 636,114 (72) | 72% |
| Siris et al          | Alendronate, risedronate            | 35,537 (65.3)         | Achieving MPR ≥80% = 43% |
| Siris et al          | Alendronate, ibandronate, risedronate | 460,584 (63.6) | 53.50% |
| Soong et al          | Alendronate                         | 32,604 (72.44)        | At 1 month, achieving MPR ≥80% = 87.6% |
|                      |                                     |                       | Achieving MPR ≥80% = 61.8% |
|                      |                                     |                       | Achieving MPR ≥80% = 28.2% |
| Suryecz et al        | Alendronate, risedronate            | 32,944 (64.3)         | 55% |
| Tafaro et al         | Alendronate, clodronate, ibandronate, risedronate | 6390 (n/a) | 53% (daily regimen) |
| Wang et al           | Alendronate, ibandronate, risedronate | 522,287 (n/a) | 70% (weekly regimen) |
|                      |                                     |                       | Achieving MPR <33% = 41.1% |
|                      |                                     |                       | Achieving MPR 34% to 65% = 21.5% |
|                      |                                     |                       | Achieving MPR >66% = 37.3% |
| Weycker et al        | Alendronate, ibandronate, risedronate | 644 (65.9) | 57% |
| Yeaw et al           | Alendronate                         | 10,268 (56.9)         | *60% |
|                      |                                     |                       | ibandronate |
| Yood et al           | Alendronate, etidronate             | 176 (63.3)            | 70.70% |
| Ziller et al         | Alendronate                         | 268,568 (63.3)        | 33% (alendronate 10 mg) |

*Mean Proportion of Days Covered (PDC). MPR, medication possession ratio.
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. Moreover, weekly oral bisphosphonates medication users had significantly higher mean persistence than those daily users. Before decreasing at ages 80 and above a number of studies have reported higher persistence and adherence at older ages than younger ages.

Similarly, the number of co-medications being received at baseline was associated with a marginally greater risk of discontinuing. Compared with male users of oral BP medications, female users were at lower odds of achieving adherence.

**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%. 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%. 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.

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. 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 and medication dosing and frequency 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. Database-derived persistence and adherence assessment carries the advantage of being objective, quantifiable and simple. 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. 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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