Reviews

Real-world Adherence and Persistence with Bisphosphonate Therapy in Postmenopausal Women: A Systematic Review

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ABSTRACT

Purpose: Bisphosphonate therapy is a well-established and effective treatment for postmenopausal osteoporosis and the prevention of osteoporotic fracture. However, poor adherence to and poor persistence with bisphosphonate therapy may reduce its benefits. Previous studies have documented the poor rates of adherence and persistence among postmenopausal women with osteoporosis. The objective of this systematic literature review was to evaluate adherence, persistence, and the impact of adherence and persistence on fracture risk in postmenopausal women with diagnosed osteoporosis.

Methods: Articles eligible for review included observational studies of the real-world use of bisphosphonates in 23 countries and were identified by using MEDLINE, EMBASE, IMSEAR (Index Medicus for South-East Asia Region), and LILACS (Latin American and Caribbean Health Sciences Database).

Findings: We identified and evaluated 10 studies that assessed bisphosphonate adherence by measuring medication possession ratio (MPR), persistence, and/or the impact of adherence and persistence on fracture risk. Mean MPR at 1 year ranged from 54% to 71% in the 3 studies that reported this assessment of adherence, and 40%–85% of patients at 1 year were adherent, defined as an MPR ≥80%, in the 8 studies that reported this end point. At 1 year, rates of persistence ranged from 28% to 74%. Rates of adherence and persistence were highest with agents requiring less frequent administration and typically declined over time. Fracture rates were significantly lower among adherent women with MPRs ≥80% compared with women with MPRs <80%.

Implications: Our results show that suboptimal adherence to and persistence with bisphosphonate therapy in postmenopausal women are common and increase the risk of fracture. Additional research is needed to identify and incorporate effective strategies for improving adherence to bisphosphonates in postmenopausal women. (*Clin Ther.* 2019;41:1576–1588)

Key Words: adherence, bisphosphonate, fracture, menopause, osteoporosis, persistence.

INTRODUCTION

Osteoporosis is a common disorder characterized by abnormalities in bone mass and the structure of bone tissue, leading to impaired skeletal strength and an increased susceptibility to fractures.[1] Most cases of osteoporosis occur in postmenopausal women.[2] Bone loss is common and rapid in the years immediately after menopause due to a reduction in circulating

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levels of estrogen, predisposing many women to osteoporosis and osteoporotic fracture.[2] In fact, in Germany, France, Italy, Spain, and the United Kingdom, ~21% of women 50−84 years of age have osteoporosis.[3,4] In postmenopausal women, osteoporotic fractures are common, cause significant morbidity and mortality, and lead to considerable economic costs.[4,5]

Although several options are available to help prevent osteoporotic fracture, bisphosphonates are effective in increasing bone density and reducing the risk of fracture, and they are typically considered first-line treatment in postmenopausal women with osteoporosis.[3,6−11] Despite the benefits of bisphosphonates, previous systematic reviews have shown that adherence to and persistence with this therapy are poor.[12,13] Suboptimal adherence to bisphosphonate therapy may reduce its benefits; studies have reported that poor adherence is associated with smaller changes in markers of bone turnover[14] and bone mass,[15] and an increase in fractures.[16] Poor adherence to bisphosphonates has also been linked to significantly higher health care resource use and economic costs.[17]

The objective of the present study was to systematically review current evidence from real-world observational studies of adherence and persistence with bisphosphonate therapy in postmenopausal women with osteoporosis, including the impact of suboptimal adherence and persistence on osteoporotic fracture. A focus on data from more recent real-world studies provides a useful update on bisphosphonate adherence and persistence and a more realistic picture of the use of bisphosphonates outside the rigid structure of clinical trials.

MATERIALS AND METHODS

The present analysis considered real-world data related to adherence and persistence with bisphosphonate therapy and the impact of adherence and persistence on patient outcomes, including clinical fracture. Real-world data were defined by using the task force designation of the International Society for Pharmacoeconomics and Outcomes Research: "data used for decision-making not collected in conventional controlled randomized trials."[18]

For the purposes of the present analysis, compliance and adherence were considered synonyms and were defined as the extent to which a patient follows the prescribed bisphosphonate regimen, including the prescribed dose and dosing interval.[19] Adherence was evaluated through calculations of the medication possession ratio (MPR), defined as the number of days of available medication divided by the total number of days in the observation period. Persistence was defined as the duration of time between the initiation and the discontinuation of therapy.

We used a broad strategy to identify relevant research, searching several databases (MEDLINE, EMBASE, IMSEAR [Index Medicus for South-East Asia Region], and LILACS [Latin American and Caribbean Health Sciences Database]) for articles published in English between January 1, 1997, and January 1, 2017, and indexed in at least 1 of the searched databases. Search terms included *osteoporosis, medication adherence*, and *patient compliance* and are described in Table I. We also searched the reference lists of the retrieved publications. Articles were considered if they evaluated adherence, compliance, and/or persistence among women with postmenopausal osteoporosis treated with bisphosphonate therapy (eg, alendronate, risedronate, zoledronate, ibandronate) living in Australia, Belgium, Brazil, Canada, Chile, France, Germany, Hong Kong, Indonesia, Israel, Italy, Malaysia, Mexico, South Africa, Singapore, South Korea, Spain, Thailand, Turkey, United Kingdom, United States, Venezuela, and Vietnam. These countries were chosen because the introduction of alternate formulations of available bisphosphonates was under consideration in these regions.

Studies were excluded if an established diagnosis of postmenopausal osteoporosis was not a specified requirement for inclusion in the article's analysis, if they included men, if they were not observational in nature, and if patients in the study received antiresorptive therapies other than bisphosphonates. Articles were also excluded if they did not use MPR as the method to evaluate adherence or did not describe the length of the permissible gap in the assessment of persistence. Abstracts, posters, and reviews were also excluded from the analysis. Duplicates were removed by using EndNote X.7.7.1, and literature was screened according to the title/abstract by using the inclusion/exclusion criteria outlined earlier. An independent reviewer resolved disagreements or discrepancies between primary reviewers.

Table I. Search terms used in all databases.

Database	Search Terms
MEDLINE	(((osteoporosis[MeSH Terms]) AND ((medication adherence[MeSH Terms] OR patient compliance[MeSH Terms]) OR (adherence[Title/Abstract] OR compliance[Title/Abstract] OR persistence[Title/Abstract]) OR ("treatment patterns"[Title/Abstract] OR "patterns of treatment"[Title/Abstract] OR "standard of care"[Title/Abstract] OR "standards of care"[Title/Abstract] OR "treatment pattern"[Title/Abstract] OR "pattern of treatment"[Title/Abstract] OR "pattern of care"[Title/Abstract] OR "patterns of care"[Title/Abstract] OR "standard care"[Title/Abstract] OR "standard treatment"[Title/Abstract] OR "standard treatments"[Title/Abstract]))) AND English[Language]) AND ("1997/01/01"[Date - Publication]: "2017/01/01"[Date - Publication])
LILACS	((mh:(osteoporose)) OR (tw:(osteoporosis))) AND (tw:(adherence OR compliance OR persistence OR "treatment patterns" OR "patterns of treatment" OR "standard of care" OR "standards of care" OR "treatment pattern" OR "pattern of treatment" OR "pattern of care" OR "patterns of care" OR "standard care" OR "standard treatment" OR "standard treatments"))
EMBASE	'osteoporosis'/exp AND ('patient compliance'/exp OR 'medication compliance'/exp OR adherence:ab,ti OR compliance:ab,ti OR persistence:ab,ti OR 'treatment patterns':ab,ti OR 'patterns of treatment':ab,ti OR 'standard of care':ab,ti OR 'standards of care':ab,ti OR 'treatment pattern':ab,ti OR 'pattern of treatment':ab,ti OR 'pattern of care':ab,ti OR 'patterns of care':ab,ti OR 'standard care':ab,ti OR 'standard treatment':ab,ti OR 'standard treatments':ab,ti) AND english:la
IMSEAR	"Osteoporosis" in Title

RESULTS

Ten studies were included in the present review. The figure illustrates the flow of and identification and inclusion of studies. Of the 3223 records identified, 236 full-text articles were evaluated and assessed for eligibility for inclusion. Two hundred twenty-six articles were excluded, primarily because patients in the study did not have an established diagnosis of osteoporosis or they were receiving bisphosphonate therapy for other conditions (n = 112). Fifty-five studies were excluded because they did not include data on adherence/persistence, 33 were excluded because patients in the study were receiving antiresorptive therapies other than bisphosphonates, 14 were excluded because they included men, 8 were excluded because they did not evaluate MPR or define the terms of persistence, 3 were excluded because they were not observational studies, and 1 was excluded due to bias in patient selection. In the study excluded due to bias, the study subjects were physicians themselves and not likely to be representative of the general population. Most studies were retrospective in nature and either involved multiple centers or involved analyses of health care databases. The quality of the studies included in the analysis differed. Although methods used to evaluate adherence and persistence varied widely among studies, adherence was typically expressed as a mean MPR or the percentage of patients with MPR $\geq$80%, which was generally considered a threshold for adherence. Persistence was typically calculated as the time between the initial filling of the prescription and the discontinuation of the medication.[12] Patients could have gaps in treatment ranging from 30 days to 1 year and still be considered persistent with bisphosphonate therapy.[13]

Table II summarizes the results of studies that used MPRs as the method to assess adherence,[16,20–28] and Table III reports the results of analyses that evaluated persistence.[16,20–23,25,28] Among the 3 studies that reported a mean MPR, the MPR at 1 year ranged from 54% to 71%, whereas 40%–85% of patients at 1 year had an MPR $\geq$80% in the 8 studies that reported this end point. At 1 year, rates of

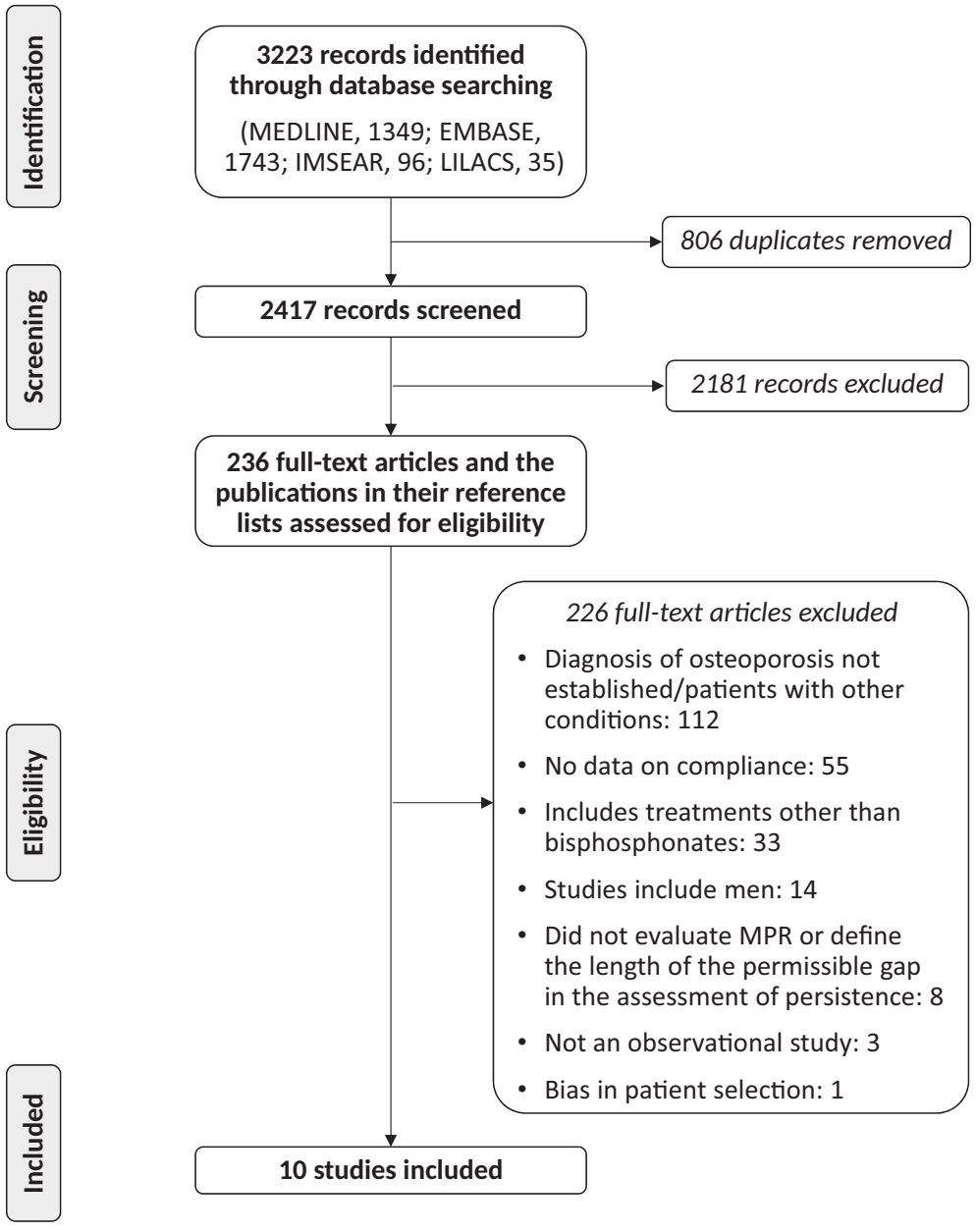

Figure. Identification, screening, and inclusion of studies. MPR = medication possession ratio.

persistence ranged from 28% to 74%. The median length of persistence ranged from 19.1 weeks (with the use of a daily regimen) to 38.4 weeks (with the use of a weekly regimen). Rates of persistence were highest with agents requiring less frequent administration (eg, agents administered weekly or monthly compared with those administered daily). As expected, rates of persistence declined over time.

Among the studies that compared daily, weekly, and monthly regimens, mean MPR was higher with monthly versus weekly regimens and with weekly versus daily regimens. The highest rates of persistence

Table II. Studies evaluating adherence with bisphosphonates in postmenopausal women.

Study (Location)	Design/Setting	Agents	Patients	Follow-up	Mean MPR	Mean MPR ≥80%
Cotte et al, 2010[20] (France)	Retrospective study using Thales prescription database with prospective follow-up	Alendronate, ibandronate, risedronate	1889 women aged ≥45 y who had received a first prescription for weekly or monthly bisphosphonate	≥6 mo	—	65.8% with weekly bisphosphonate; 74.1% with monthly bisphosphonate
Dugard et al, 2010[21] (United Kingdom)	Retrospective study using pharmacy claims data	All bisphosphonates	254 women aged >50 y	5 y	—	44.0% at 1 y; 23% at 5 y
Ferguson et al, 2016[22] (United Kingdom)	Retrospective medical record database of data collected by general practitioners	Oral bisphosphonates	36,320 postmenopausal women aged ≥50 y	12 mo to >36 mo	—	85.1%
Hadji et al, 2012[23] (Germany)	Retrospective study using IMS Disease Analyzer database	Oral bisphosphonates	4217 women (10.7% were aged ≤60 y and 89.3% were aged >60 y)	At least 2 y	—	51%
Shehadeh-Sheeny et al, 2013[24] (Israel)	Cross-sectional, multicenter survey	Oral bisphosphonates	303 postmenopausal women aged >60 y	1 y	—	41.3%
Cramer et al, 2005[25] (United States)	Retrospective study using a claims database representative of insured US population	Alendronate, risedronate	2741 women aged >45 y and new to bisphosphonates	1 y	Overall, 60.6%; Daily use, 57.6%; Weekly use, 69.2%	—
				1 y	53.5%	—

Table II. (*Continued*)

Study (Location)	Design/Setting	Agents	Patients	Follow-up	Mean MPR	Mean MPR ≥80%
Eisenberg et al, 2015[26] (United States)	Retrospective study using a claims database	Alendronate, risedronate, ibandronate	27,905 women aged ≥55 y with ≥1 bisphosphonate claim			
Modi et al, 2015[27] (United States)	Retrospective study using a claims database	Oral bisphosphonates	62,446 women aged ≥50 y	1 y	—	43.0%
Rabenda et al, 2008[28] (Belgium)	Retrospective study of a prescription claims database	Alendronate daily or weekly	29,157 women aged >45 y and new to bisphosphonate therapy	1 y	Overall, 64.7% Daily use, 58.6% Weekly use, 70.5%	Overall, 48.1% Daily, 40.4% Weekly, 57.0%
Siris et al, 2006[16] (United States)	Retrospective study using commercial claims database and Medicare databases	Alendronate, risedronate	6391 women aged ≥45 y	2 y	—	47.0%

MPR = medication possession ratio.

Table III. Studies evaluating persistence with bisphosphonates in postmenopausal women.

Study (Location)	Agents	N	Follow-up	Length of Permissible Gap*	Median Length of Persistence	Percent Persistent
Rabenda et al, 2008[28] (Belgium)	Alendronate (daily or weekly)	54,807	6–12 mo	5 wk	35.7 wk	6 mo, 58% 12 mo, 40%
Cotte et al, 2010[20] (France)	Ibandronate, risedronate, alendronate	1889	≥6 mo	45 d for monthly formulations; 30 d for weekly formulations	37.9 wk (monthly use); 24.1 wk (weekly use)	6 mo, 57.3%, monthly use; 45.7%, weekly use 12 mo, 47.5%, monthly use; 30.4%, weekly use
Dugard et al, 2010[21] (United Kingdom)	All bisphosphonates	254	5 y	12 mo	—	1 y, 74% 5 y, 50%
Ferguson et al, 2016[22] (United Kingdom)	Oral bisphosphonates	36,320	12 mo to >36 mo	3 mo	—	<12 mo, 26.1% 12 to <24 mo, 20.2% 24 to <36 mo, 16.1% ≥36 mo, 37.7%
Hadji et al, 2012[23] (Germany)	Oral bisphosphonates	4217	≥2 y	30 d	20.8 wk	1 y, 27.9% 2 y, 12.9%
Cramer et al, 2005[25] (United States)	Alendronate, risedronate	2741	1 y	30 d	38.4 wk (weekly use) 19.1 wk (daily use)	12 mo, 44.2%, weekly use; 31.7%, daily use
Siris et al, 2006[16] (United States)	Alendronate, risedronate	6391	2 y	30 d	—	24 mo, 23%

*The permissible gap is length of time allowed between refills. A patient with a lapse in therapy beyond the permissible gap is considered to have discontinued therapy.

were consistently observed among users of monthly bisphosphonates, whereas the lowest rates of persistence were observed with daily regimens.

Table IV reviews the results of studies that evaluated the association between adherence and/or persistence and the rate of clinical osteoporotic fracture.[16,22,23,26–28] In these studies, the incidence of osteoporotic fracture among bisphosphonate users was analyzed according to their MPR. Results indicate that the risk of osteoporotic fractures was considerably lower in adherent patients than in nonadherent patients and among patients who persisted on bisphosphonate therapy compared with those who discontinued it. Among individuals with MPRs ≥80%, the rate of osteoporotic fracture was significantly lower than among patients with MPR <80%. Fracture rates were also ~60% lower among persistent patients compared with patients who discontinued therapy.

DISCUSSION

Overall, available research indicates that approximately one third to one half of postmenopausal women with osteoporosis are nonadherent to bisphosphonate therapy. Moreover, after 1 year, only 28%–74% remain persistent on their prescribed treatment. These results are clinically important due to the significant association between poor adherence and poor persistence and increased risk of fracture, use of health resources, risk of hospitalization, and significant economic costs.[17,26,29]

Factors that contribute to poor adherence and suboptimal persistence with preventive interventions include sociodemographic characteristics, health beliefs and psychosocial characteristics, condition-related factors such as concomitant medications and comorbidities, therapy-related factors such as adverse events and tolerability, and health system–related factors such as prescription coverage and provider–patient relationship.[30–32] Important determinants of adherence with oral bisphosphonates are typically issues related to dosing and adverse events, including the timing of dosing and the need to fast before dosing.[32,33] Treatment options that avoid the inconvenience of fasting, offer simple dosing schedules, and are easily accessible may improve adherence with antiresorptive therapy.[33] For example, the use of an enteric-coated formulation of risedronate that incorporates a calcium chelator (EDTA, a widely used food stabilizer) may help eliminate the need for fasting without affecting the efficacy or bioavailability of risedronate.[33,34]

Due to the numerous factors that affect adherence to and persistence with bisphosphonate therapy, addressing the challenge of poor adherence and poor persistence requires multifaceted and comprehensive solutions. Poor adherence is a universal problem for most therapies used to manage chronic conditions. In one study, the percentages of patients achieving adherence rates ≥80% during the first year of drug therapy were 51.2% in patients with osteoporosis, compared with 72.3% in patients with hypertension, 65.4% in patients with type 2 diabetes, 54.6% in patients with hypercholesterolemia, and 36.8% in patients with gout.[35] Possible solutions for improving adherence unrelated to the choice of therapy include improved communication between health care providers and patients as well as using social and informational tools such as social networks, mobile phone apps, and text messaging.[32,36]

Our review has some limitations. Studies assessed in the review used heterogeneous methods of defining and reporting adherence and persistence, which can make it difficult to compare and interpret findings. There was also significant variability among the populations and databases used in the analyses. Another important limitation is the exclusion of studies from countries such as India, Russia, and Japan, as well as most countries in South America, Europe, and Africa. Nonetheless, an assessment of the results from studies excluded due to their geographic region or their study design indicates that the results of these studies are consistent with the results of our analysis.[37–40] For example, a database-based study from the Netherlands (N = 8822) reported that 58% of female new users of bisphosphonates had an MPR ≥80% at 1 year and that women with an MPR <80% had a 45% increase in the risk of fracture compared with those with an MPR ≥80%.[37]

The studies included in our review were limited to those that specified a diagnosis of osteoporosis, and therefore another limitation of our analysis was the exclusion of studies of postmenopausal women using bisphosphonate therapy that did not specify a diagnosis of osteoporosis as an inclusion criterion. Moreover, because our search strategy did not include the names of specific bisphosphonates, it is possible that some relevant research may have been

Table IV. Studies associating adherence and/or persistence rates with fracture risks in postmenopausal women using bisphosphonates.

Study (Location)	Agents	N	Fracture Type	Fracture Risk Ratio According to Persistence Level	Fracture Risk Ratio According to MPR Comparison
Rabenda et al, 2008[28] (Belgium)	Alendronate (daily or weekly)	47,868 (1280 fracture)	Hip	HR, 0.404; 95% CI, 0.36−0.46 ($P < 0.0001$) for persistent patients vs nonpersistent patients	—
Ferguson et al, 2016[22] (UK)	Oral bisphosphonates	36,320	Any osteoporotic fracture	HR, 2.25; 95% CI, 1.35−3.77 ($P = 0.002$) for patients with <12 mo persistence vs patients with 24 to <36 mo persistence	—
Hadji et al, 2012[23] (Germany)	Oral bisphosphonates	4217	Any fracture	—	Percentage of patients without fracture, 88.1% in patients with MPR >80% vs 85.0% in those with MPR ≤80% ($P = 0.016$)
Modi et al, 2015[27] (United States)	Oral bisphosphonates	62,446	Fragility fracture	—	3.2% of patients with MPR ≥80% or MPR ≥60% in year 1 experienced a fracture in year 2 vs 3.3% of patients with an MPR <80% and 3.4% of patients with an MPR <60%
Siris et al, 2006[16] (United States)	Alendronate and risedronate	6391	Osteoporotic fracture	—	Adjusted fracture risk 22% lower for patients with MPR ≥80% vs those with MPR <80%; odds ratio, 0.777 (95% CI, 0.719−0.839)
		27,905	Total fracture	—	

Table IV. (*Continued*)

Study (Location)	Agents	N	Fracture Type	Fracture Risk Ratio According to Persistence Level	Fracture Risk Ratio According to MPR Comparison
Eisenberg et al, 2015[26] (United States)	Alendronate, risedronate, ibandronate				Fracture rates were 3.3% in patients with MPR <70% and 2.4% for those with MPR ≥70% at 13−24 mo and 6.0% and 4.8%, respectively, at 25−36 mo ($P < 0.001$ for both comparisons)

HR = hazard ratio; MPR = medication possession ratio.

inadvertently excluded from our analysis. Given the frequency use of the term "bisphosphonate" in studies of this therapeutic class, however, including specific drug names as search terms may not have altered our findings. We also did not consider studies that only evaluated the proportion of days covered, another commonly used assessment of adherence, and not MPR, although studies that evaluated proportion of days may also have included assessments of MPR or persistence.[41–45] In addition, exactly how the diagnosis of osteoporosis was established was not always clear, although most studies in our analysis specified that the diagnoses were established by using diagnostic codes, densitometry, or reports of an osteoporotic fracture.[16,21,23,25,27,28]

Another important limitation is the nature of results obtained from analyses of retrospective claims databases. The utility of retrospective analyses of claims databases is determined by the information included in those databases. Data from these databases do not provide certainty that patients who picked up their prescriptions actually took their medications as prescribed. In addition, true rates of adherence and persistence may be lower because research indicates that ~30% of patients who are prescribed drugs never fill or pick up their prescriptions.[46] In addition, the methodologic quality of the studies included in our analysis varied.

Despite these limitations, the present review provides a useful and novel summary of adherence to and persistence with bisphosphonate therapy in the real world among women with postmenopausal osteoporosis.

CONCLUSIONS

Despite the established clinical benefits of bisphosphonates in postmenopausal women with osteoporosis, adherence and persistence with bisphosphonates are suboptimal in this population. Poor adherence and persistence are associated with poor outcomes, including an increased risk of fracture. Due to the aging of the population and the clinical burden of osteoporotic fracture, addressing the challenge of poor adherence in postmenopausal women is vital. Additional research is needed to determine which interventions are associated with increased adherence and to determine the most effective and cost-effective tools for improving adherence in women using antiresorptive therapies.

Potential options include multidisciplinary approaches involving easier-to-use formulations, computerized alerts and reminders, and patient engagement programs.

CONFLICTS OF INTEREST

Dr. Fardellone is a consultant for Expanscience and UCB, and a speaker for Amgen, Lilly, Mylan, and Teva. Dr. de Sá Moreira, Mr. de Oliveira, and Mr. Julian are employees of Kantar, which was contracted by Teva to perform the systematic review. Dr. Tang was an employee of Teva during the time of the study. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

A Teva employee (Dr. Tang) was involved in study design, analysis and interpretation of data, writing of the manuscript, and the decision to submit the manuscript for publication.

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Dr. Tang, Dr. de Sá Moreira, Mr. de Oliveira, and Mr. Julian conceived and designed the experiments, and Dr. de Sá Moreira, Mr. de Oliveira, and Mr. Julian performed the experiments. All authors analyzed and interpreted the data, contributed resources, wrote and revised the paper, and were involved in the decision to submit for publication. All authors approved the manuscript in its final form.

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