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REVIEW ARTICLE

A systematic review of factors affecting medication adherence among patients with osteoporosis

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Abstract

Summary The aim of this review was to identify factors that influence patients' adherence to anti-osteoporotic therapy. Factors identified that were associated with poorer medication adherence included polypharmacy, older age, and misconceptions about osteoporosis. Physicians need to be aware of these factors so as to optimize therapeutic outcomes for patients.

Introduction To identify factors that influence patients' adherence to anti-osteoporotic therapy.

Methods A systematic review of literature was performed for articles published up till January 2018 using PubMed®, PsychINFO®, Embase®, and CINAHL®. Peer-reviewed articles which examined factors associated with anti-osteoporotic medication adherence were included. Classes of anti-osteoporotic therapy included bisphosphonates, parathyroid hormone-related analogue, denosumab, selective estrogen receptor modulators, estrogen/progestin therapy, calcitonin, and strontium ranelate. Meta-analyses, case reports/series, and other systematic reviews were excluded. Identified factors were classified using the World Health Organization's five dimensions of medication adherence (condition, patient, therapy, health-system, and socio-economic domains).

Results Of 2404 articles reviewed, 124 relevant articles were identified. The prevalence of medication adherence ranged from 12.9 to 95.4%. Twenty-four factors with 139 sub-factors were identified. Bisphosphonates were the most well-studied class of medication ($n = 59$, 48%). Condition-related factors that were associated with poorer medication adherence included polypharmacy, and history of falls was associated with higher medication adherence. Patient-related factors which were associated with poorer medication adherence included older age and misconceptions about osteoporosis while therapy-related factors included higher dosing frequency and medication side effects. Health system-based factors associated with poorer medication adherence included care under different medical specialties and lack of patient education. Socio-economic-related factors associated with poorer medication adherence included current smoker and lack of medical insurance coverage.

Conclusion This review identified factors associated with poor medication adherence among osteoporotic patients. To optimize therapeutic outcomes for patients, clinicians need to be aware of the complexity of factors affecting medication adherence.

Keywords Anti-osteoporotic therapy · Medication adherence · Osteoporosis · Patient compliance · Bisphosphonates

Introduction

Osteoporosis is a prevalent public health problem which afflicts over 54 million adults in the USA [1]. Globally, osteoporosis has been implicated in nine million fractures [2]. With the aging population and increased lifespan, the annual prevalence of osteoporosis-related fractures is expected to increase [3]. Medication adherence refers to the extent to which a person takes their medication as prescribed by their healthcare professional. Non-adherence to anti-osteoporotic therapy has been linked with increased risk of fractures as well as healthcare costs [4]. Importantly, osteoporotic fractures have been associated with increased mortality, morbidity, and healthcare costs. Of note, a Swedish study found that fractures contribute to 0.5 billion Euros in healthcare costs annually [5].

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Commonly used classes of anti-osteoporotic treatment include bisphosphonates, parathyroid hormone analogues, denosumab, and selective estrogen receptor modulators. These therapies vary in costs, side effect profiles, dosing frequencies, and routes of administration, which have differing implications on medication adherence [6]. A study by McHorney et al. showed that the presence of symptomatic side effects from oral bisphosphonate therapy was significantly associated with poorer medication adherence [7]. Pertaining to dosing frequency, data from literature has been conflicting. While a study showed that lower frequency of medication dosing was the strongest predictor of adherence to bisphosphonate therapy [8], another study showed no difference in medication adherence rates between weekly and monthly therapy [9]. Adherence to anti-osteoporotic therapy is also affected by other factors such as patients' beliefs, demographics, and comorbidities [10]. Notably, the perceived lack of benefits from anti-osteoporotic treatment was identified in several studies as a common reason for non-adherence [7, 11, 12].

The multitude of factors that affect medication adherence confounds the ability of healthcare professionals to formulate effective interventions to improve outcomes for patients with osteoporosis. Reviews available in literature have only examined medication adherence rates and related outcomes in selected patient populations or among patients on specific drug therapies [4, 13]. To our best knowledge, there is no review performed which has summarized factors affecting medication adherence among patients with osteoporosis. Hence, the aim of this review is to identify and present factors influencing patients' adherence to anti-osteoporotic therapy.

Methods

A search of literature was conducted in four online databases which included PubMed®, PsychINFO®, Embase®, and CINAHL®. Keywords utilized for the search included (Osteoporosis OR Osteoporoses OR age-related bone loss) AND (medication OR drug OR treatment OR medicine OR therapeutics OR therapy) AND (adherence OR compliance OR persistence OR non-compliance OR non-adherence) AND (factors OR barriers). In addition, hand-searches of references listed in related articles were performed. The literature review was current as of January 2018 with no restriction of articles' start date.

Two reviewers (CT Yeam and HCC Tan) performed independent evaluation of the articles for inclusion and discussed where discrepancies occurred. Where discrepancies could not be resolved, further discussion was made with a third independent reviewer (JJB Seng).

The review included full-text, original articles published in English which examined usage of anti-osteoporotic treatment in both male and female patients aged 18 years old or more. Classes of treatment examined included bisphosphonates, parathyroid hormone-related analog, denosumab, selective estrogen receptor modulators, estrogen/progestin therapy, calcitonin, strontium ranelate, and calcium and vitamin D-related supplementation. We excluded meta-analyses, case reports, case series, and other systematic reviews.

Factors related to medication adherence that were identified from articles were grouped into categories as per World Health Organization (WHO) recommendation [14]. The five main categories were, namely, patient-related, therapy-related, condition-related, health system, and socio-economic factors. A human model for treatment adherence in patients with osteoporosis was proposed to aid physicians in better visualizing factors that impacted treatment adherence.

Results

A total of 2404 articles were retrieved from PubMed®, PsychINFO®, Embase®, and CINAHL® as shown in Fig. 1. After excluding 591 duplicated articles, a further 1722 articles were excluded for the following reasons: 1497 articles were irrelevant based on title and abstract; 100 articles were not full papers; 93 articles were meta-analyses, case reports, and systematic reviews; and 32 articles were not in English. After 33 additional articles were identified and added from reference search, a total of 124 articles were included and reviewed. Bisphosphonates were the most well-studied class of medication ($n = 59$, 48%), and most of the studies were conducted in Europe ($n = 51$, 41%), North America ($n = 42$, 34%), and Asia ($n = 23$, 18%). The prevalence of medication adherence across all studies ranged from 12.9 to 95.4%. Among randomized controlled trial (RCT) studies, the rates of medication adherence in ranged from 37.3 to 67.0%. A total of 24 factors with 139 sub-factors were identified and categorized into five categories based on the WHO's five dimensions of adherence. The types and number of studies that presented for and against each specific factor were presented below. A pie chart (Fig. 2) was utilized to represent the frequency of sub-factors investigated in the studies included. Patient-related factors (29%) were the most commonly studied domain across all studies, followed by therapy-related domain (27%) and condition-related domain (27%). Details pertaining to the characteristics of included studies are reported in Supplementary Table 1.

Condition-related factors

Table 1 shows condition-related factors which were associated with poorer or better medication adherence. A total of three main factors with 35 sub-factors were identified, which were, namely, "past medical history," "comorbidities," and "medical screening for osteoporosis" (Table 1). Common past medical

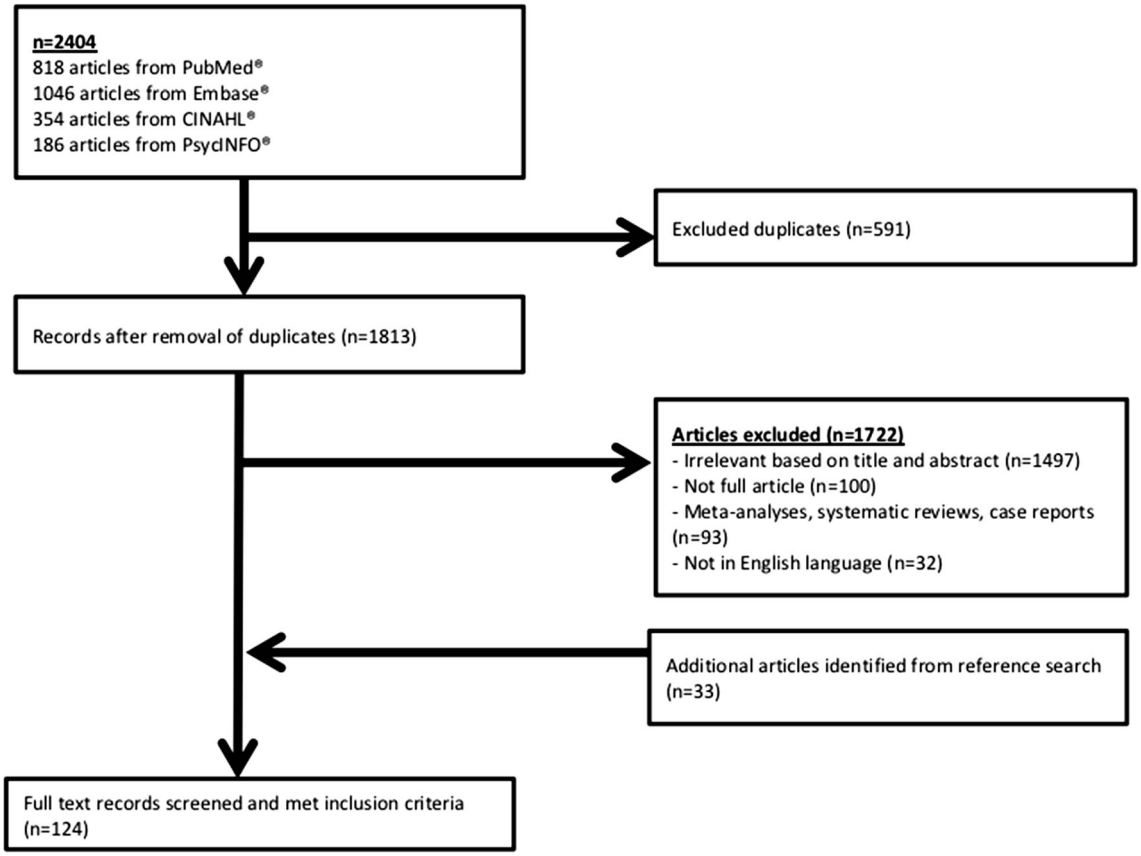

Fig. 1 Flow chart for inclusion of articles for review

history factors associated with higher medication adherence included history of falls or fractures [9, 24–36, 52], while factors associated with poorer medication adherence included receiving concomitant treatment for comorbidities [26, 28, 32, 33, 44, 45, 47–49, 59] and having psychiatric conditions such as depression [9, 15, 32, 33, 50, 58]. Osteoporotic screening was also associated with better osteoporotic medication adherence [16, 25, 38, 45, 52, 58, 64, 66].

Patient-related factors

Table 2 shows patient-related factors which were associated with poorer or better medication adherence. Six main factors with 36 sub-factors were identified, which were, namely, "patient demographics," "physical and mental function," "menopausal-related," "disease and treatment related," "family history," and "others" (Table 2). Demographic factors associated with poorer medication adherence included having lower education levels [6, 10, 40, 44, 47, 57, 66, 75, 80]. Factors related to physical and mental functions included lower levels of physical activity [44, 86, 87]. Higher age of menopause was shown to be associated with poorer medication adherence [26, 59, 88]. Among factors related to disease and treatment perceptions, misconceptions about osteoporosis [43, 65, 80, 87, 89–95] and the lack of perceived benefit of therapy [30, 41, 43, 48, 64, 81, 88, 93, 95, 96] were shown to lower medication adherence.

Therapy-related factors

Table 3 shows therapy-related factors which were associated with poorer or better medication adherence. Five therapy-related factors with 31 sub-factors were identified which included "medication dosing regimen," "medication side effects," "type of osteoporotic medication," "other medication-related factors," and "past osteoporotic medication history." Regimen factors affecting medication adherence included higher dosing frequency [8, 31, 45, 49, 51, 52, 54, 61, 71, 76, 77, 87, 98–108]. The development of medication-related side effects [7, 23, 28, 44, 48, 59, 64, 65, 88, 89, 91–93, 97, 109, 111–114] was associated with poorer medication adherence.

Health-based system factors

Table 4 shows health system-based factors which were associated with poorer or better medication adherence. A total of seven health system-based factors with 16 sub-factors were identified, namely, "healthcare provider"- and "healthcare facilities"-related factors. Healthcare provider factors associated

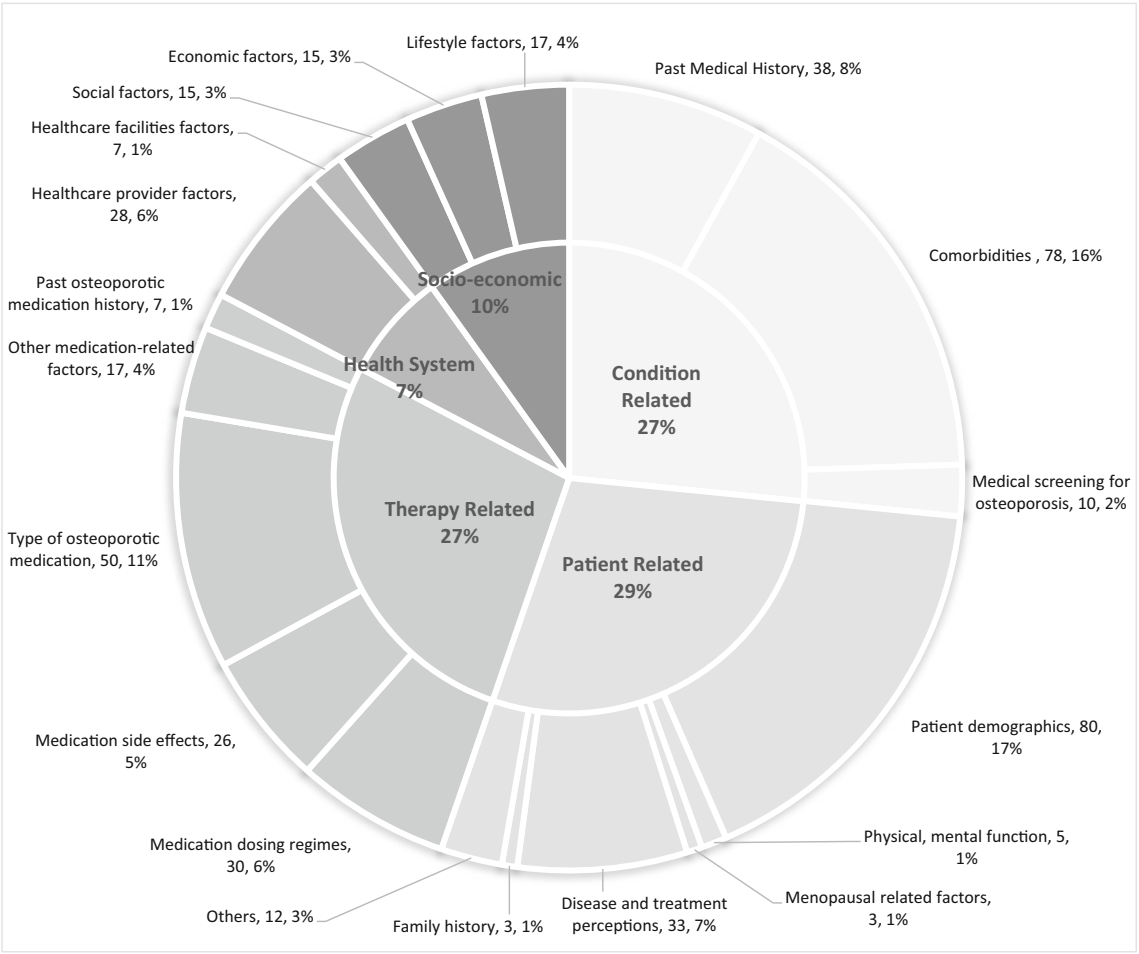

Fig. 2 Pie chart representing frequency of studies in the five main categories

with poorer medication adherence included care under different medical specialities [16, 19, 22, 26, 34, 60, 116]. In addition, healthcare facility factors associated with poorer medication adherence included poor accessibility to medication [89, 91, 111].

Social-economic factors

Table 5 shows social-economic factors which were associated with poorer or better medication adherence. Three socio-economic factors with 21 sub-factors were elucidated, which were "social," "economic," and "lifestyle" factors. Social factors associated with poorer medication adherence included location of residence [6, 28, 44, 58]. Economic factors such as higher treatment costs [53, 67, 91, 92] were associated with poorer medication adherence. Lifestyle factors such as smoking [17, 28, 30, 44, 57, 64, 86, 126, 127] were also found to be associated with poorer medication adherence.

Femur model for medication adherence among osteoporosis patients

Incorporating the five broad categories of factors that affects adherence to anti-osteoporotic medication, a femur model for medication adherence, as depicted in Fig. 3, was proposed to aid clinicians in remembering the factors and applying it in their daily clinical practice.

Discussion

This is a systematic review which has evaluated literature extensively for factors that affect medication adherence among patients with osteoporosis. To our best knowledge, it is also the first review which provided an overview of the types and number of studies that supported or disagreed with the factors investigated.

Table 1 Condition-related factors and their association with poorer adherence/persistence/compliance to medication therapy

Factors	No. of supporting studies	Type of studies	No. studies that disagree	Type of studies
Past medical history				
History of falls, fractures	10	C [6, 15–20], CS [21], O [22], RCT [23]	16	C [6, 9, 24–35, 52], CS [36]
History of treatment/medications for comorbidities	1	C [37]	3	C [33, 37, 38]
Longer disease duration of osteoporosis			3	C, [28, 39], CS [36]
Higher number of previous falls, fractures	1	C [17]		
History of adverse drug events from comorbidities	1	C [40]		
Menopause	1	C [41]		
Intact uterus	1	C [42]		
Vaccination (Flu)	1	C [43]		
Comorbidities				
Receiving concomitant treatment/medications for comorbidities (yes/no)	12	C [6, 26, 28, 31–33, 44–46], CS [47], O [48], OComS [49]	8	C [6, 7, 19, 31, 46, 50, 51], CS [10]
Higher number of concomitant medications for comorbidities	7	C [6, 8, 20, 38, 52–54]	2	C [43, 55]
Having gastrointestinal diseases (hepatobiliary, liver, malabsorption syndrome, digestive problems, Inflammatory bowel disease, celiac disease, mucositis)	7	C [32, 33, 38, 51, 56], CS [57], O [48]		
Psychiatric conditions (depression, mental disorders)	6	C [9, 15, 32, 33, 50], O [58]	1	C [55]
Metabolic diseases (diabetes, hypertension, hyperlipidemia)	5	C [32, 33, 46, 52], OCS [59]	1	C [16]
Autoimmune diseases (rheumatoid arthritis, inflammatory joint disease)	4	C [33, 45, 52, 60]	1	C [61]
Cardiovascular diseases (coronary artery disease, myocardial infarction, heart failure)	2	C [6, 33]	3	C [16, 43, 62]
Higher number of comorbidities	4	C [25, 52, 60], CS [59]		
Having general comorbidities	2	C [40], L [63]	2	C [17], CS [10]
Neurological diseases (dementia, Parkinson, stroke)	1	C [46]	2	C [6, 45]
Orthopedic diseases (arthrosis, osteopenia, metabolic bone disease)	2	C [7], CS [59]		
Respiratory diseases (COPD, chronic pulmonary disease)	1	C [16]		
Collagen diseases	1	C [6]		
Presence of medication side effects arising from comorbidity treatment	1	CS [64]		
Longer duration of having rheumatoid arthritis			1	C [61]
Presence of symptoms (pain; daily, climacteric)			1	C [50]
Medical screening for osteoporosis				
Presence of osteoporosis screening	2	CS [64], Q [65]	8	C [16, 25, 38, 45, 52, 66, 67], O [58]

C cohort, *CS* cross-sectional, *FGD* focused group discussion, *LQS* longitudinal qualitative study, *O* observational, *ComS* comparative study, *Q* qualitative, *RCT* randomized controlled trial, *L* longitudinal

The rate of anti-osteoporotic medication adherence was found to be highly varied across studies and ranged from 12.9 to 95.4%. Potential reasons for this high variability could be attributed to the differences in the characteristics of patient populations and the tools used for assessing adherence. While real-world medication adherence rates were anticipated to be lower, there appeared to be no significant differences in adherence rates in randomized controlled trials compared to non-randomized studies. Some of the tools used for evaluating medication adherence included patient self-reporting, electronic prescription filling records, and pharmacy clinical records, which have their inherent strengths and limitations. Proportion of days covered (PDC) has been recommended as the "gold standard" calculation method for evaluating

Table 2 Patient-related factors and their association with poorer adherence/persistence/compliance to medication therapy

Factors	No. of supporting studies	Type of studies	No. studies that disagree	Type of studies
Patient demographics				
Older age	20	C [9, 17, 20, 24, 25, 28, 41, 42, 46, 53, 68–73], CS [10, 32, 57, 74]	21	C [6, 27, 31, 35, 37, 39, 43, 50–52, 62, 66, 75–79], CS [64, 80, 81], L [63]
Male gender	11	C [6, 19, 25, 37, 46, 68, 69, 72, 77, 82, 83]	2	C [27, 52]
Lower education levels	9	C [6, 40, 44, 66, 75], CS [10, 47, 57, 80]		
Race (non-white vs White, African-Americans vs others, Hispanic vs White, Asian vs White)	7	C [19, 25, 28, 44, 67, 73], RCT [84]	1	C [56]
Higher body mass index	3	CS [57, 59], RCT [84]	1	C [56]
Marital status (single vs married)	2	C [6], CS [80]	1	C [85]
Shorter height	1	C [56]		
Marital status (previously married vs married)	1	C [75]		
Physical and mental function				
Lower levels of physical activity	3	C [44, 86], CS [87]		
Poorer mental health status	1	CS [87]		
Increased forgetfulness	1	Q [65]		
Menopausal-related factors				
Higher age of menopause	2	C [26], CS [59]	1	C [88]
Disease and treatment perceptions				
Misconception/ill-informed about osteoporosis	11	C [43, 89, 90], CS [80, 87, 91, 92], Q [65, 93, 94], RCT [95]		
Lack of perceived benefit of therapy	11	C [7, 30, 41, 43, 88, 96], CS [64, 81], O [48], Q [93], RCT [95]		
Lack of concern for consequences of osteoporosis	4	C [39, 43], CS [87], Q [65]		
Having more concerns about therapy	3	CS [64, 81], O [48]	1	CS [36]
Poor attitude towards treatment	1	C [43]		
Lack of perceiving osteoporosis as a disease	1	Q [94]		
Lack of perceived self-efficacy in medication use	1	CS [64]		
Family history				
Family history of osteoporosis			2	C [26], Q [93]
Family history of osteoporosis-related fracture			1	OLNRS [97]
Others				
Lower level of tertiary care facilities utilization	2	C [46, 55]	3	C [6, 19, 46]
Lower level of primary care services and facilities utilization	2	C [25, 55]	3	C [19, 25, 52]
Loss of height since youth			1	C [56]
No loss of height after osteoporosis			1	Q [94]

C cohort, *CS* cross-sectional, *Q* qualitative study, OLNRS open-label non-randomized study, *RCT* randomized controlled trial, *O* observational study, *L* longitudinal

medication adherence in long-term therapies [128]. However, this was not assessed in studies included in this review. Future studies should hence consider using this tool to assess medication adherence rates among patients with osteoporosis. More importantly, the heterogeneity observed reflects the complex nature of medication adherence and highlighted the need for identification of pertinent factors affecting medication adherence. This will in turn facilitate the development of targeted interventions to improve medication adherence.

Among condition-related factors, receiving concomitant medication for comorbidities was found to be associated with poorer medication adherence. Managing complex medication

Table 3 Therapy-related factors and their association with poorer adherence/persistence/compliance to medication therapy

Osteoporotic treatment Factors	No. of supporting studies	Type of studies	No. studies that disagree	Type of studies
Medication dosing regimen				
Higher dosing frequency	21	C [8, 31, 45, 51, 52, 54, 61, 71, 76, 77, 98–106], CS [87], ComS [49]	2	C [107, 108]
Complex instructions for medication administration	4	C [89, 109], Q [94, 110]		
Complex medication regimen	2	CS [87], OLT [111]		
Use of treatment dose vs preventive dose			1	C [71]
Medication side effects				
Presence of medication side effects (GI)	20	C [7, 23, 28, 44, 88, 89, 109, 112, 113], CS [64, 91, 92, 114], O [48], Q [65, 94, 110], OLT [97, 111], LQS [93]		
Type of osteoporotic medication				
Use of bisphosphonates (CLOD, alendronate, etidronate, risedronate) vs non-bisphosphonates	6	C [6, 26, 69, 79, 115], ComS [41]	7	C [6, 25, 34, 56, 67, 99, 115]
Use of SERM (raloxifene) vs non-SERM	3	C [76, 79, 105]	6	C [28, 34, 52, 115], CS [116], ComS [41]
Use of supplements (calcium, vitamin D, multivitamin)	3	C [61], CS [44, 92]	4	C [27, 45, 79, 117]
Use of HRT (estrogen, progesterone) vs non-HRT	2	C [9, 25]	5	C [28, 32, 52, 118], CS [114]
Use of calcitonin vs non-calcitonin	4	C [9, 25, 28, 115]	2	C [52, 115]
Type of bisphosphonates (ibandronate, risedronate, zoledronic acid vs alendronate, ibandronate)	3	C [53, 62, 105]	2	C [72], OLT [119]
Use of PTH (teriparatide) vs non-PTH	2	C [28, 115]	2	C [85, 115]
Use of anti-RANKL antibody (denosumab) vs non-anti-RANKL antibody	1	C [115]	2	C [50, 120]
Use of strontium ranelate vs non-strontium ranelate	2	C [76, 79]		
Other medication-related factors				
Switch of anti-osteoporotic medication during therapy	3	C [44, 68, 121]	3	C [16, 77, 98]
Longer duration of anti-osteoporotic therapy	1	CS [114]	3	C [62], CS [10, 87]
Generic vs branded osteoporotic medication	2	C [83, 122]	1	C [77]
Higher osteoporotic medication cost	2	C [82], O [48]		
Prompt treatment initiation after diagnosis			1	C [50]
Previous osteoporotic treatment failure			1	C [17]
Past osteoporotic medication history				
History of anti-osteoporotic treatment	1	C [108]	6	C [22, 56, 58, 72, 104, 117]

C cohort, *CS* cross-sectional, *FGD* focused group discussion, *LQS* longitudinal qualitative study, *O* observational, *ComS* comparative study, *Q* qualitative, *CT* controlled trial, *L* longitudinal, *NRCT* non-randomized controlled trial, *OLT* open-label trial

dosing regimens and instructions can be challenging for patients prescribed with polypharmacy, and this in turn contributes to poor medication adherence [129]. In the recent years, deprescribing of unnecessary medications has been suggested as an avenue to reduce polypharmacy and improve medication adherence [130]. Physicians should hence consider reviewing the medication lists of patients regularly and withdraw unnecessary medication therapies, so as to improve medication adherence among patients. Additionally, psychiatric disorders such as depression were found to be associated with poor medication adherence among patients with osteoporosis. Similar findings have been observed in studies evaluating medication adherence in patients with other chronic conditions such as diabetes mellitus, ischemic heart disease, and rheumatoid arthritis [131–133]. A meta-analysis done by Grenard et al. showed that depressed patients were twice more likely to be non-adherent to their chronic disease medication than patients without depression, which was noted consistently across disease types [133]. Interestingly, there is growing evidence which suggests that depression has an unfavorable

Table 4 Health system-based factors and their association with poorer adherence/persistence/compliance to medication therapy

Factors	No. of supporting studies	Type of studies	No. studies that disagree	Type of studies
Healthcare provider factors				
Physician-specific factor				
Prescription by non-specialist (GPs vs specialists)	5	C [26, 27, 31, 55], Q [94]	5	C [26, 60, 62, 69, 123]
Care under different medical specialty (orthopedic, family, metabolism, rehab medicine, oncology, gynecology vs rheumatology/others)	6	C [16, 19, 26, 34, 60], ComS [116]	1	C [22]
Male physician	1	C [58]		
Lesser years of work experience	1	C [55]		
Trust in physician				
Dissatisfaction with physician visits	1	Q [94]		
Communication and support from healthcare providers				
Lack of patient education (information sharing, counseling from healthcare professional, lack of information exchange and explanations from healthcare professionals, failure to emphasize importance of adherence)	5	C [82, 101], CS [92], Q [65, 110]		
Lack of support from healthcare professionals (encouragement, managing side effects)	1	LQS [93]		
Lack of patient support programs (specialist fracture programs)			2	C [22], RCT [23]
Healthcare facilities factors				
Access to medication/medication facilities				
Poor accessibility to medication/medical facilities/pharmacies	3	C [89], CS [91], OLT [111]	1	C [79]
Restrictive drug formularies	1	C [54]		
Healthcare policies/plans				
Lack of healthcare plan design (indemnity, point of service plans, preferred provider organizations vs health maintenance organizations)	1	C [8]		
Type of healthcare facilities				
Receiving care in specialty care centers (internal medicine/rheumatology/endocrinology vs general hospital)			1	C [72]

C cohort, *CS* cross-sectional, *FGD* focused group discussion, *LQS* longitudinal qualitative study, *O* observational, *ComS* comparative study, *Q* qualitative, *RCT* randomized controlled trial, *OLT* open-label trial

effect on bone health, and is associated with an increased risk of osteoporotic fractures [134]. Depression has been shown to increase the production of pro-inflammatory cytokines such as interleukin-6 and TNF-α, which in turn leads to higher bone resorption [134]. Furthermore, it has also been shown to stimulate the hypothalamic–pituitary–adrenocortical axis, contributing to hypercortisolemia and increased bone loss [134]. Given the prevalence of depression among patients with chronic diseases such as osteoporosis and its negative consequences on patients' health, appropriate screening and treatment of depression might aid in improving medication adherence among patients with osteoporosis.

Among patient-related factors, patients with misconceptions about osteoporosis and lack of perceived benefit of therapy were found to be associated with lower adherence to anti-osteoporotic medications. On a similar vein, the lack of patient education and support from healthcare professionals were associated with poorer medication adherence. Although the usage of phone reminders and targeted education sessions by healthcare professionals have been explored as potential interventions to improve medication adherence, data pertaining to their outcomes has been either conflicting or poor. A randomized controlled study by Cooper et al. showed that reminder phone calls from nurses to educate patients about osteoporosis medication and the importance of medication adherence led to a significant increase in medication adherence rates [119]. However, another randomized controlled trial by Bianchi et al. found that the provision of phone reminders and targeted educational programs for patients was not effective in improving compliance to anti-osteoporotic therapy [135]. A potential reason for the above findings could be due to the differences in anti-osteoporotic dosing regimens and frequency of phone

Table 5 Social-economic factors and their association with poorer adherence/persistence/compliance to medication therapy

Factors	No. of supporting studies	Type of studies	No. studies that disagree	Type of studies
Social factor				
Location of residence (city vs rural areas; Canada: Quebec vs Ontario; USA: Midwest, south, west vs northeast/others)	4	C [6, 28, 44, 58]	2	C [6, 124]
Unemployment	2	C [6, 85]	1	C [6]
Lack of caregiver	1	LQS [93]		
Lower education	1	CS [125]		
Having children at home	1	C [6]		
Staying close to hospital	1	C [6]		
Live alone and in rural areas	1	CS [57]		
Poor family support	1	O [48]		
Economic factors				
Lower income level	5	C [6, 20, 75], CS [125], OLT [111]		
No/lower statutory insurance or subsidy	4	C [27, 62, 98, 124]	1	Q [94]
Higher treatment costs (co-payment)	4	C [53, 67], CS [91, 92]		
Not receiving pension	1	C [98]		
Lifestyle factors				
Current smoker	9	C [17, 28, 30, 44, 86, 126, 127], CS [57, 64]		
Alcohol consumption	2	C [43], CS [57]	1	C [28]
Lower level of physical activity	2	C [28, 30]		
Former smoker	1	C [86]		
Making lifestyle changes	1	CS [92]		
Treatment regimen adapted to patient's lifestyle			1	CS [87]

C cohort, *CS* cross-sectional, *FGD* focused group discussion, *LQS* longitudinal qualitative study, *O* observational, *ComS* comparative study, *Q* qualitative, *RCT* randomized controlled trial, *OLT* open-label trial

reminders utilized in the two studies. While Cooper et al. utilized monthly phone call reminders for patients on monthly bisphosphonate therapy, the latter study included patients on daily, weekly, and monthly bisphosphonate therapy for which 3-monthly phone reminders were made. Hence, there may remain a potential role of utilizing frequent reminder phone calls to reinforce compliance among patients with poor medication adherence, although more studies should be conducted.

Among the therapy-related factors identified, our review found that higher dosing frequency of anti-osteoporotic medication and adverse side effects were associated with poor adherence among patients. For instance, a study by Goldshtein et al. found that the most common reason cited for discontinuation of oral bisphosphonates was due to gastrointestinal side effects such as heartburn and gastric reflux [81]. Hence, physicians should consider mitigating potentially avoidable side effects before initiation of therapy, by providing patient counseling on how to minimize the side effects of medications or even consider alternative route of drug administration (e.g., bisphosphonates). Additionally, regular evaluation and management of adverse effects associated with anti-osteoporotic

Fig. 3 Femur model for factors affecting anti-osteoporotic medication adherence

medication should be performed by physicians on follow-up visits. A systematic review by Hiligsmann et al. found that simplification of dosing regimens has the most significant impact on improving medication adherence and persistence among patients with osteoporosis [136]. Hence, physicians should also endeavor to simplify medication dosing regimens where appropriate, to improve patients' adherence to medication.

High treatment cost was one of the main socio-economic factors found to be associated with poorer medication adherence. The financial condition of patients should be assessed by physicians when prescribing anti-osteoporotic medications which are more expensive. For example, the annual cost of teriparatide is US$6700 as compared to alendronate acid which costs US$900 per year [137]. For patients requiring financial assistance, they should be referred to channels such as hospital social services for help where appropriate.

In this review, the five broad categories of medication adherence factors were incorporated in the proposed femur model. Each section of the model represents a domain of factors that clinicians should keep in mind during their daily practice when prescribing anti-osteoporotic medication for patients.

There were several limitations that should be considered when interpreting the findings. Firstly, while a total of 139 sub-factors were identified, the aggregate magnitude of each factor on medication adherence among patients with osteoporosis was not assessed. This should be explored in future meta-analysis. Additionally, while the search terms and strategy were designed to cover a comprehensive base of literature, the omission of potentially relevant articles could not be ruled out. Steps taken to minimize this included utilizing unrestricted search dates in the databases and hand-searching of references listed in the related articles.

Conclusion

In conclusion, through a systematic review of the literature available, factors which were associated with poorer anti-osteoporotic medication adherence were identified, of which several are potentially modifiable. These findings will aid researchers and clinicians in directing future research efforts to optimize medication adherence and outcomes for patients with osteoporosis. This would be of utmost importance with the aging population worldwide, which would see a rise in the number of patients with osteoporosis.

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Compliance with ethical standards

Conflicts of interest None.

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