Osteoporosis treatment preferences and satisfaction in postmenopausal women: Denosumab compared with oral bisphosphonates

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KEYWORDS

osteoporosis treatment, bisphosphonates, Denosumab, adherence, satisfactions.

ABSTRACT

Aim
This paper aims to investigate whether Denosumab is more effective in promoting adherence and satisfaction than oral bisphosphonates in the treatment of osteoporosis in postmenopausal women.

Methods
Electronic database - MEDLINE, PubMed, CINAHL, Wiley online Library, ProQuest Nursing and Allied Health), free text engines Google Scholar and Findit@Flinders and reference lists of retrieved papers were searched according to the inclusion and exclusion criteria. Twelve studies were ultimately selected.

Primary argument
The author analyses and critically appraises literature comparing two common osteoporotic medications: oral bisphosphonates and subcutaneous Denosumab in view of patients' preferences and satisfaction. Findings from this review could provide suggestions for developing frameworks in clinical practice, identify strategies to improve patient adherence to treatment and develop policies promoting active patient involvement in treatment decision-making.

Results
Following thematic organisation of the studies, four major themes emerged: patient's view on attributes on osteoporotic medications; patient satisfaction and preferences in oral bisphosphonates compared to Denosumab; adherence to treatment with oral bisphosphonates compared to Denosumab; and practice implications.

Conclusion
Findings from reviewed studies favor Denosumab over oral bisphosphonates as the preferred long-term treatment in postmenopausal women. Patients have a greater satisfaction with less frequent dosing, mode of administration and side effects of Denosumab.

INTRODUCTION

Osteoporosis is a severe and chronic condition with significant physical and emotional concerns including increased risks of fragility fractures, hospitalisation and often surgery needs, chronic pain and high mortality rates (Perry and Downey 2011). It causes a tremendous burden on people affected by the disease, their families, as well as the health and social care system (Ebeling et al 2013). Numerous pharmacological agents are designed to slow disease progression and prevent complications with the effectiveness of some reported by many robust clinical trials (Conn et al 2015). However, studies have shown that 50-75% of patients treated with anti-osteoporotic medications have discontinued treatment within one year. This sub-optimal adherence rate and lack of persistence with prescribed treatment leads to a significant decrease (approximately 50%) in the effectiveness of these treatments (Rosen and Drezner 2015; Reynolds et al 2014), and consequently success in achieving therapeutic goals and successful control of osteoporosis (Cairoli et al 2015; Cheng et al 2013; Ziller et al 2012; Imaz et al 2010).

When making decisions regarding treatment options, in order to decrease the likelihood of failure, we must have a better understanding and knowledge of the reasons behind the non-adherence to treatments. Identifying the determinants could assist in clinical decision-making and development of guidelines and policies (Cairoli et al 2015; Laba 2014). According to Rabenda and Reginster (2010), the biggest barriers (most often reported by patients) in relation to discontinuing treatment are: inconvenience, complicated and strict medications dosing regime, and gastrointestinal side effects with oral therapy. However, since osteoporosis treatment is available in various forms, dosages, frequency of administration and regimens, medical practitioners and patients should choose the most appropriate, convenient and personalised treatment (Ward et al 2013; Barbosa et al 2012; Lee et al 2011).

REVIEW OF THE LITERATURE

Methodology

An integrative style of review was chosen as most appropriate to address the research question. An appraisal tool developed by McMaster University 'Critical Review Form for Quantitative Studies' was used to evaluate the retrieved articles (Law et al 1998). The review is organised thematically, allowing important findings from the research to be grouped into themes, followed by further discussion in terms of the topics covered.

Search strategy

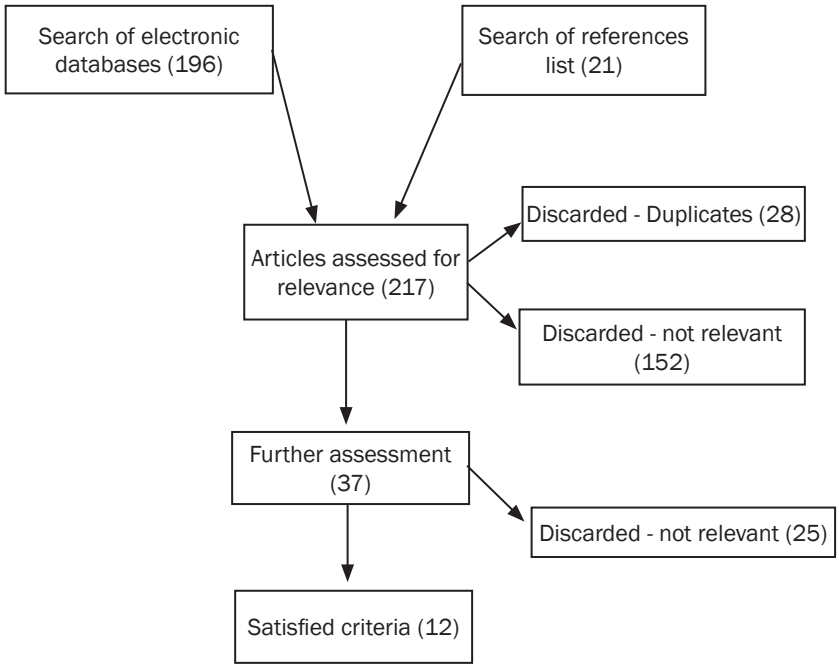
A comprehensive search of electronic databases including MEDLINE, PubMed, CINAHL, Wiley online Library, ProQuest Nursing and Allied Health, identified studies providing answers to the research question. Free text search engines such as Google Scholar and Findit@Flinders were extensively used to search through various sources and related publications. Additionally, reference lists of retrieved papers were scrutinised; primarily focusing on previously published systematic reviews and meta-analyses, which often cite important high quality papers. Both titles and subsequent abstracts were screened for eligibility. Only primary studies published in English, in full text, and between 2010 and 2015 were chosen where the articles' main focus was on comprising and reporting outcomes of adherence, preference and patient satisfaction with oral bisphosphonates as opposed to subcutaneous Denosumab. This review only includes studies with postmenopausal women - the largest osteoporosis prevalence group.

Systematic reviews, meta-analyses and other forms of reviews were excluded. Articles comparing cost effectiveness were also excluded, as this review focuses on patient views and opinions. Studies with participants living in aged care or health institutions were also excluded, as these medications are not self-administered, instead reliance is highly dependent on health care providers.

Search outcome

Twelve articles met the inclusion and exclusion criteria and were selected for evaluation of strengths and weaknesses in view of answering the review question, as well as providing suggestions for possible benefits to clinical practice and improvement of treatment outcomes. All articles have a quantitative design, six are randomised clinical trials and six are cohort studies.

Figure 1: Flow chart of literature search



RESULTS

All of the selected studies clearly indicated the research aim and used appropriate methodology to address the research question. Participant selection was appropriate to study design, which included large samples, carried out in accordance to ethical guidelines. All studies also provided clear statements of findings, research values and clinical practice relevance. Although randomised trials are highly ranked in the hierarchy of evidence (National Health and Medical Council (NHMRC) 2009), the five trials were open-label and not blinded, potentially leading to biased results. The majority of the studies had a clinical trial setting where third-party influence, willingness to participate in study or study design cannot rule-out selection biases. Freemantle et al (2012), Kendler et al (2011) and Kendler et al (2014) used the same sample in their studies therefore as independent studies their findings could provide significant research value, however in the context of this review they were considered as one source of evidence. All studies had short 1-2 years durations, which is potentially an inadequate period to evaluate adherence to treatment or patient's satisfaction for this chronic disease, which requires extended treatment.

Summary of selected articles

A summary of the selected studies is presented in table 1.

Table 1: Summary of reviewed articles

Study	Aim	Sample	Method	Major findings	Strengths and limitations
Barrett-Connor et al (2011).	Association between treatment satisfaction and persistence with postmenopausal osteoporotic treatment.	2,405 postmenopausal women	Assessment of satisfaction using Treatment Satisfaction Questionnaire for Medication (TSQM).	Lower satisfaction with treatment increased risk of discontinuation. Effectiveness, side effects and convenience play important role in adherence to treatment.	Large sample, anonymous questionnaire, data from longitudinal study, primary care setting. Loss to follow up, self-reporting persistence.
Brown et al (2014).	Compare the effect on bone mineral density (BMD) and bone turnover in patients who switched therapy from bisphosphonates to denosumab.	1703 postmenopausal women.	Post-hoc analyses of 2 reviously randomised, open-label, parallel-group studies.	Denosumab more effective in increasing BMD and reducing bone turnover.	Large sample, randomisation. Clinical trial compliance in real-world could be lower. Selection bias - participants willingness to be involved in study. Open-label study.
Freemantle et al (2012).	Provide final results of the DAPS (Denosumab Adherence Preference Satisfaction) 2 years study.	250 postmenopausal women.	Randomized, open-label, multicentre study; Crossover; used Preference & Satisfaction Questionnaire (PSQ).	Preference and satisfaction higher for denosumab than alendronate. 92.4% preferred injections over oral medications as more convenient, better mode and frequency ofadministration.	Randomisations, multicentre, frequent follow ups. Not a real-world setting.
Hadji et al (2015).	Evaluate denosumab-taking behaviour in routine practice.	1500 postmenopausal women from 4 European countries.	Interim analyses of multicenter, prospective, non-interventional study.	87.0-95.3% were persistent and 82.7-89.3% were adherent with treatment. Understanding patients and physicians factors influencing medications taking may improve persistence with treatment.	Large sample, multicentre, 4 health systems. Heterogeneity of clinics, physicians and participants. Participants and physicians willingness to participate in trials.
Hiligsmann et al (2014).	Evaluation of preferences for Medications properties and how patients exchange these properties.	257 postmenopausal women.	Quantitative study Discrete Choice Experiment (DCE) survey: efficacy, side effect, mode, frequency, cost to patient.	Patients prefer higher efficacy lower cost and less frequent dosing regimens. Dislike GI side effects more than skin reaction or flu like symptoms; Willing to pay more and give up on efficacy for treatment mode.	Participants exposed to different types of treatment previously. Possible selection bias. Only common side effects included in questionaries.
Kendler et al (2010).	Compare patient preference and satisfaction between denosumab and alendronate.	1,693 postmenopausal women.	Quantitative, international, randomised, double-blind, DECIDE and STAND; PSQ used.	Higher preference and satisfaction with less frequent treatment.	Large sample, international, randomised, double-blind, double-dummy, phase 3 head-to-head studies- Selection bias-participants willingness to be involve in study. Not real-world setting. Short duration of the study.

Kendler et al (2011).	Assess adherence to treatment with 6 monthly denusemab and weekly alendronate.	250 postmenopausal women from 25 centres.	Randomized, open-label, multicentre, crossover study; follow up at 6, 12, 18 and 24 months; Beliefs about Medications Questionnaire (BMQ).	Denosumab higher adherence, satisfaction and preference in dosing and route of administration routine compared to alendronate.	Randomisations, multicentre, frequent follow ups, equal exposure to 2 treatments, adequate length of study. Not a real-world setting.
Kendler et al (2014).	Analysis how adherence to treatment is influenced by articipants belief in treatment, necessity of treatment, their concerns and preferences.	250 postmenopausal women from 25 centres.	Quantitative study Post-hoc analyses of two randomised, open-label studies; TSQM used with 4 domains: effectiveness, side effects, convenience, and global satisfaction.	Denosumab - greater necessity, preferences and adherences. Greater satisfaction with denosumab as more effective and convenient.	Randomisations, multicentre, frequent follow ups. Not real-world setting. Negative media reports for alendronate and positive for denosumab.
Palacios et al (2015).	Evaluate the treatment satisfaction when switching from bisphosphonates to denosumab.	1703 postmenopausal women.	Randomised, open-label, parallel-group study.	Greater satisfaction may improve adherence to treatment and consequently effectiveness of the therapy.	Randomisation, large sample.Post-hoc analysis, Open-label. Short 1 year study. Potential self-selection bias.
Roux et al. (2014).	Compare efficacy and safety of denosumab and risedronate.	870 postmenopausal women from 82centres.	Questionnaire - efficacy, safety, convenience and direct cost to patient. MaxDiff analysis was used to determine preferences.	Denosumab is more effective and safer option when compared with risedronate.	Randomised, international, multicentre, large sample. Selection bias large numbers of exclusion. Open-label and short 1 year study. Clinical trial only.
Silverman et al (2013).	Assess weighting of osteoporotic medication attributes - safety, efficacy, cost and convenience.	367 postmenopausal women from 4 ethnic groups.	Multicentre, single arm, prospective, observational study. PSQ and BMQ used.	Efficacy and safety have higher attributes than cost and convenience.	Comprehensive questionnaire. Heterogeneity of participants. Not consistent with entering answers.
Silverman et al (2015).	To estimate persistence with donesumab treatment.	935 postmenopausal women.	Interim analyses after 12 months of 24 months study.	81.9% persistent at 12 months. High persistence with treatment have potential in improving treatment.	Prospective observational study, multicentre, real-world setting. Heterogeneity of clinics, physicians.

MAJOR THEMES

Following thematic organisation of selected studies, four major themes emerged: patient's view on attributes of osteoporotic medications; patient's satisfaction and preferences in oral bisphosphonates compared to Denosumab; adherence to treatment in oral bisphosphonates compared to Denosumab; and implications to practice.

Theme 1: Patient's view on attributes on osteoporotic medications

Five of the chosen studies evaluated the importance of osteoporotic medication attributes from the patient's perspective. 'Drug efficacy', 'safety', 'out-of-pocket cost', 'convenience' were key features selected by participants (Palacios et al 2015; Hiligsmann et al 2014; Silverman et al 2013; Barrett-Connor et al 2012; Freemantle et al 2012). Hiligsmann et al (2014), using a Discrete-Choice Experiment (DCE), asked patients to rank two types of medications in relation to these attributes and concluded that 'effectiveness', was the highest attribute and 'cost' was the lowest. A 'longer dosing regimen' was selected as more significant than 'the mode of administration', and 'gastrointestinal side effects' was the most troublesome. Similarly the results of a study by Silverman et al (2013) show that 'drug efficacy' is the most valued feature followed by 'safety', 'cost' and 'convenience' while also observing that medication ranking depended on age, education and income, but not on racial differences.

Barrett-Connor et al (2012) used the Treatment Satisfaction Questionnaire for Medication (TSQM). In their study, 'side effects' were classed as the most important attribute with 'global satisfaction' being the lowest. 'Side effects' were ranked as the highest trigger of discontinuing treatment, followed by 'inconvenience'. Palacios et al (2015) also used the TSQM tool, however their outcome revealed that 'side effects' were not the major contributor in choosing medication, with 'effectiveness' and 'convenience' valued higher. In most of the studies, the 'effectiveness' of medications was valued highest, followed by 'safety'. Other factors such as 'out-of-pocket cost' and 'convenience', which include mode and frequency of administration of medications, were ranked as important but not essential.

Theme 2: Patient's satisfaction and preference in oral bisphosphonates vs Denosumab

Six of the studies from different countries and health care systems acknowledged patient satisfaction and their preferences to treatment as significant determinants when choosing osteoporosis treatment options (Palacios et al 2015; Hiligsmann et al 2014; Kendler et al 2014; Freemantle et al 2012; Kendler et al 2011; Kendler et al 2010). To evaluate patient satisfaction and preference, researchers used the Patients Satisfaction Questionnaire (PSQ), TSQM or the Belief in Medication Questionnaire (BMQ). The 'convenience and life style fit', 'mode of administration', 'dosing frequency' and 'drug related side effects' were revealed as the most influencing factors affecting participant's satisfaction level. Freemantle et al (2012) showed that 91% of participants were satisfied with injections while only 52% preferred oral medication for 'medications administration mode'. Similarly, 94% preferred injection and only 43% chose tablets in view of 'frequency of administrations'. Less frequent treatments were preferred as reported by Kendler et al (2010), revealing that 64% participants preferred bi-annual injections and 16% favoured weekly tablets. Approximately 20% of patients were indifferent to frequency.

Results from a study by Hiligsmann et al (2014) showed that a significant number of participants preferred bi-annual injections to weekly tablets but there were no noteworthy dissimilarities in preferences between bi-annual injections and monthly tablets, proving that less frequent treatment regimens were preferred. Patients often blame lifestyle inconvenience for discontinuing osteoporotic treatments (Kendler et al 2014). In all six studies, a bi-annual Denosumab injection was recognised as more convenient over oral bisphosphonates primarily due to the less frequent treatment requirements. Possibility of side effects related to treatment of

osteoporosis were of high concern which were also reported in all selected studies but according to Palacios et al (2015) it was not always crucial. Gastrointestinal side effects, often associated with oral bisphosphonates, were recognised as more troublesome than skin infections and flu-like symptoms sometimes associated with Denosumab (Hiligsmann et al 2014).

Theme 3: Adherence and persistence to treatment in oral bisphosphonates versus Denosumab

Five of the selected papers examined factors influencing patient adherence to treatment (Kendler et al 2014; Barrett-Connor et al 2012; Freemantle et al 2012; Kendler et al 2011; Kendler et al 2010). Barrett-Connor et al (2012) and Kendler et al (2014) concluded that a patient's belief in the necessity of therapy and fear of possible side effects plays a significant role in treatment adherence; a higher degree of necessity with a lower degree of concern leads to better treatment adherence. In two widely recognised studies, DECIDE and STAND (Kendler et al 2010), patients were initiated or switched to therapy with Denosumab from oral bisphosphonates. The authors reported that persistence with treatment was high, above 90% and was very similar in both groups. Those results however could be overestimated, as all patients were closely monitored, possibly motivating them and consequently improving their adherence. Similarly, another study, DAPS, in which participants were randomly divided into two groups 'Alendronate' and 'Denosumab', showed that after the first year, adherence to Denosumab was considerably higher than to Alendronate; 87.3% and 76.6% respectively. Furthermore, after a crossover treatment, adherence to Denosumab increased to 92.5% and Alendronate dropped to 63.5% (Kendler et al 2014; Freemantle et al 2012; Kendler et al 2011).

Generally, high adherence to Denosumab was also confirmed in the study by Hajdi et al (2015) and Silverman et al (2015). The interim result of the non-interventional study in four European countries showed that 82.7-89.3% of women were adherent to being treated with Denosumab, because they received their second injection within the required time (Hajdi et al 2015). Similarly, 82% of postmenopausal women from a study by Silverman et al (2015) (Canada and USA), who were treated with Denosumab as a routine osteoporosis therapy, were persistent with their treatment, and obtained a second dose of the medication within six months. A significant advantage of both of these studies is that they were realistic real-world studies, minimising the likelihood of biases.

Theme 4: Practice Implications

Findings from the reviewed studies highlight the importance of an individual's beliefs, preferences and satisfactions in clinical decision-making regarding treatments to improve osteoporosis care. This 'patient-centred care' or 'preference based care' approach suggested by researchers provides valuable evidence for health care providers and policy makers regarding which treatments and attributes are more respected and preferred, and emphasises that patients and doctors might have different opinions about treatment choices (Palacios et al 2015; Silverman et al 2015; Barrett-Connor et al 2012). A large body of evidence shows that patient preferences in regards to 'frequency regime' and 'mode of administration' must be taken into account to deliver personalised treatment and improve treatment outcome. Less frequent medications administration regime are viewed as more 'convenient' to fit into a patient's lifestyle therefore, bi-annual injections are preferred by many post-menopausal women with osteoporosis (Hadji et al 2015; Palacios et al 2015; Brown et al 2014; Hiligsmann et al 2014; Kendler et al 2014; Roux et al 2014 Silverman et al 2013; Freemantle et al 2012; Kendler et al 2011; Kendler et al 2010).

Injectable medications, like Denosumab, require additional health services but they also provide great opportunities for health care providers to communicate with patients, motivate them with treatment and directly assess treatment adherence (Freemantle et al 2012). Hiligsmann et al (2014) revealed that patients are willing to trade 'efficacy of treatment' and have 'out-of-pocket expenses' for their preferred choice.

Researchers also suggest that for patients who were non-adherent with weekly oral bisphosphonates, switching to monthly regime is not as effective as switching to Denosumab bi-annually (Palacios et al 2015; Brown et al 2014). Understanding the factors influencing patient adherence to treatment at the commencement of their therapy may significantly improve treatment outcomes (Hadji et al 2015; Kendler et al 2014). Consequently, there is a great need for increased research into methods of increasing patient's knowledge and awareness of different options available for them, assessing their preferences and techniques of reducing side effects (Palacios et al 2015; Kendler et al 2014; Barrett-Connor et al 2012).

DISCUSSION

The purpose of this review is to explore available literature examining the effect of patient satisfaction and treatment preferences in relation to treating osteoporosis in postmenopausal women by comparing oral bisphosphonates and Denosumab. The findings support the existence of strong links between patient satisfactions and treatment adherence, also revealing that the main reasons for poor adherence are inconvenience, complicated dosing regime and side effects. The reviewed studies highlight the importance of personalised individual's choices, preferences and satisfactions in clinical decision-making regarding treatment to improve care (Hadji et al 2015; Palacios et al 2015; Silverman et al 2015; Freemantle et al 2012.

When comparing the two reviewed treatments, both have 'pros and cons'; oral bisphosphonates require a strict regime in order to achieve optimal effect and minimise the risk of side effects (Roux et al 2014) while administration of medication via injections often requires frequent visits to a clinic and can also be associated with pain and needle phobia (Kendler et al 2010). Patient safety was considered a significant treatment attribute and a common reason for discontinuing treatment (Cairoli et al 2015; Hiligsmann et al 2014; Barrett-Connor et al 2012). Possible gastrointestinal side effects from oral bisphosphonates are more bothersome than flu-like symptoms or skin infections from Denosumab (Hiligsmann et al 2014; Kendler et al 2014; Barbosa et al 2012).

Hiligsmann et al (2015) suggested that patient beliefs and preferences need to be addressed to improve medication adherence. Patient satisfaction plays a crucial role in treatment adherence; women who reported low satisfaction are 37% more likely to discontinue or switch the treatment than those who have a higher satisfaction (Palacios et al 2015). According to Barret-Connor et al (2012) this number may be even higher, up to 67%. Although those two factors are very important when choosing the best treatment option, other medication attributes such as effectiveness, safety and cost of treatment are also highly recognised by patients and may influence their decision (Cairoli et al 2015; Hiligsmann et al 2014; Kendler et al 2014; Freemantle et al 2012). According to current guidance and recommendations for treatment of osteoporosis in postmenopausal women, oral bisphosphonates are the first option because of their effectiveness, affordability and significant safety data (Rosen and Drezner 2015). However, our findings show that Denosumab, when compared with oral bisphosphonates, has been proven more effective in improving BMD in all routinely measured sites, significant reduction in bone turnover as well as in preventing fractures in numerous rigorous trials (Roux et al 2014; Recknor et al 2013; Sutton and Riche 2012). Although research shows that the cost of Denosumab is slightly higher than oral bisphosphonates, it is more beneficial in long-term practice because bi-annual injections provide better treatment adherence and optimisation (Parthan et al 2013; Barbosa et al 2012; Hiligsmann and Reginster 2011).

Randomisations, large samples, use of widely recognised tools in analyses of findings, and high relevance to practice are the most significant strengths of the reviewed studies. The main limitation discovered throughout the appraisal was diversity in design of studies, which could decrease transferability, or generalisability of the results. The majority of chosen studies were clinical trials potentially resulting in selection bias. Most

studies were open-label, participants were willing to be involved, understood the purpose and were aware that their adherence is monitored therefore their adherence to treatment might be higher. Moreover, participants had regular contacts with healthcare providers, which could be a motivational factor enhancing adherence. Additionally, cost of medications, travel expenses to clinics, follow-ups and diagnostic tests were all covered eliminating out-of-pocket expenses. Large diversity within participant's characteristics such as age, education, and socioeconomic status, cultural and ethnical differences, high and low fracture risk can be seen as both strengths and weaknesses.

Another significant limitation was the short duration of trials. All studies occurred over one or two years, therefore participants taking Denosumab bi-annually had only two treatment doses and were subsequently classified as adherent to treatment and treatment satisfaction was evaluated only on those two doses. The studies only focused on frequent but minor side effects, with rare but major adverse reactions omitted.

Further research using a well-designed observational study (prospective or retrospective cohort studies) and longitudinal studies would be beneficial in addressing patient satisfaction and adherence to treatment in real-world settings and potentially minimising bias (Gibson and Glenny 2012).

Despite limitations, the findings from this review may assist healthcare providers in better understanding the reasons for poor treatment adherence for osteoporosis and other chronic diseases. Usually, there is no single reason for discontinuing treatment therefore it would be unrealistic to believe that one intervention may resolve the problem and thus, strategies for improving adherence should be individualised (Rabenda and Reginster 2010). Fung and Spector (2010) emphasised the need for support and education for health practitioners and patients to ensure informed decision-making. They also advocated tailored treatment management to suit the specific patients' needs.

CONCLUSION

Findings from these selected studies favor Denosumab over oral bisphosphonates as the preferred long-term treatment in postmenopausal women. Patients have a greater satisfaction with less frequent dosing as well as the mode of administration of Denosumab. Similarly, because oral bisphosphonates are more likely to cause troublesome side effects, patients were more satisfied with Denomusab than oral bisphosphonates. Thus, Denosumab has a high potential to improve adherence to treatment of osteoporosis in postmenopausal women. However, limited research in this field and insufficient studies in 'real-world' settings reduce the value of these outcomes. Therefore, further research is needed to provide more substantial evidence leading to informed practice recommendations.

However, and more significantly, selected studies highlight the importance of understanding an individual's personal beliefs, preferences and overall satisfaction when making clinical decisions regarding treatment choices. Medication-taking decisions should be rational and informed with good understanding of personal preferences. The single intervention, like prescribing Denosumab instead of oral bisphosphonates, will not alienate problems with low treatment adherence. Therefore, future interventions, guidelines and policies should encourage healthcare providers to customise treatment management to suit the individual patient and co-operate with all parties involved in the development of guidelines and recommendations to improve the effectiveness of treatment for osteoporosis.

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