



TITLE: Denosumab and Zoledronic Acid for Patients with Postmenopausal Osteoporosis: A Review of the Clinical Effectiveness, Safety, Cost Effectiveness, and Guidelines

DATE: 11 September 2012

CONTEXT AND POLICY ISSUES

Osteoporosis is characterized by low bone mineral density (BMD), deterioration of bone microarchitecture, and a consequent increase in bone fragility and risk of fracture.¹ Osteoporosis is most prevalent in postmenopausal women over 50 as estrogen levels decline.^{2,3} The World Health Organization (WHO) estimates that 10% of 60 year old women, 20% of 70 year old Women, and 40% of 80 year old women worldwide have osteoporosis.² In Canada, postmenopausal osteoporosis affects more than 1.5 million women.⁴

BMD is determined by the delicate balance of bone resorption (osteoclast activity) and bone formation (osteoblast activity), with osteoporosis occurring when bone resorption exceeds bone formation.³ There are several therapies available for the prevention and management of postmenopausal osteoporosis. Nitrogen-containing bisphosphonates are highly potent inhibitors of osteoclastic bone resorption and have proven to be effective at reducing vertebral fracture risk.⁵ Bisphosphonates such as alendronate and risedronate have been used for treatment of postmenopausal osteoporosis for many years and are taken orally with a daily dosage regimen.⁵ Zoledronic acid (Aclasta) is a newer bisphosphonate administered intravenously once-yearly.⁶

Recent advancements in the field of bone biology have led to the development of a new class of postmenopausal osteoporosis therapy. Denosumab (Prolia) is a human recombinant monoclonal antibody that binds to RANKL, a protein that acts as an essential mediator of osteoclast formation, thereby inhibiting osteoclast formation, function, and survival.^{7,8} Denosumab is administered subcutaneously at six-month intervals.^{3,7-9} Due to the complex dosing regimen of oral bisphosphonates, compliance rates may be low, making therapies such as zoledronic acid and denosumab attractive treatment options.¹⁰

Both denosumab and zoledronic acid have received recommendations for listing, with criteria, within Canada's publicly funded drug plans by the Canadian Expert Drug Advisory Committee (CEDAC) and the Canadian Drug Expert Committee (CDEC), respectively. The committees recommend that denosumab and zoledronic acid be listed for women with postmenopausal

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osteoporosis who meet two of the following criteria: 1) aged 75 years or older; 2) have had a previous fragility fracture; or 3) a BMD T-score ≤ -2.5 , or more than 2.5 standard deviations below the mean peak bone mass.^{11,12} In addition, the patient must be contraindicated for bisphosphonate therapy due to hypersensitivity or abnormality of the esophagus.^{11,12} Actual listing criteria of the various provincial, territorial, and federal drug plans may vary. Despite these criteria, there is limited evidence on the efficacy and harms of using denosumab and zoledronic acid as a second-line therapy for postmenopausal women with intolerance or inadequate response to oral bisphosphonates.⁴

The purpose of this review is to examine the clinical evidence regarding the use of denosumab (Prolia) and zoledronic acid (Aclasta) in patients with postmenopausal osteoporosis who have discontinued oral bisphosphonates or are experiencing further decline while on treatment with oral bisphosphonates. In addition, the evidence on compliance rates of postmenopausal osteoporosis patients taking oral bisphosphonates will be examined.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of denosumab and zoledronic acid for patients with postmenopausal osteoporosis who have discontinued oral bisphosphonates or are experiencing further decline while on treatment with oral bisphosphonates?
2. What is the clinical evidence on the safety and harms of denosumab and zoledronic acid for patients with postmenopausal osteoporosis who have discontinued oral bisphosphonates or are experiencing further decline while on treatment with oral bisphosphonates?
3. What is the cost effectiveness of denosumab and zoledronic acid for patients with postmenopausal osteoporosis who have discontinued oral bisphosphonates or are experiencing further decline while on treatment with oral bisphosphonates?
4. What are the evidence-based guidelines regarding treatment for patients with postmenopausal osteoporosis who have discontinued oral bisphosphonates or are experiencing further decline while on treatment with oral bisphosphonates?
5. What is the evidence on the compliance rate of patients with postmenopausal osteoporosis taking oral bisphosphonates, zoledronic acid, or denosumab?

KEY MESSAGE

Denosumab and zoledronic acid were shown to be safe and effective in patients with postmenopausal osteoporosis who have switched from oral bisphosphonates, though whether these patients experienced decline or were intolerant of oral bisphosphonate therapy is unclear. Compliance rates are generally inadequate in patients taking oral bisphosphonates and improved in patients on denosumab therapy. Clinical practice guidelines recommend that zoledronic acid, denosumab, strontium ranelate, or calcitonin be used to treat patients who are intolerant to oral bisphosphonate therapy. No evidence for the cost effectiveness of denosumab or zoledronic acid in patients experiencing decline on oral bisphosphonate treatment was identified.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type, except for question #4 (guidelines filter was applied). Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and May 30, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with postmenopausal osteoporosis <ul style="list-style-type: none"> - Patients who discontinued bisphosphonates due to gastrointestinal issues, esophageal abnormalities, etc. - Patients experiencing further decline in bone mineral density while being treated with bisphosphonates
Intervention	Zoledronic acid (Aclasta) or denosumab (Prolia)
Comparator	Oral bisphosphonates Other osteoporosis treatments No treatment
Outcomes	Clinical efficacy, safety and harms, cost effectiveness, guidelines and recommendations, compliance rate
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), observational studies (safety and compliance only), economic evaluations, evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in a selected systematic review, or were published prior to 2007.

Critical Appraisal of Individual Studies

The quality of included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.¹³ The quality of RCTs and non-randomized studies were evaluated using the Downs and Black instrument.¹⁴ Guidelines were assessed for quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument.¹⁵ A numeric score was not calculated for each study. Instead, strengths and limitations of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 549 citations. Upon screening titles and abstracts, 521 citations were excluded and 28 potentially relevant articles were retrieved for full-text review. An additional six potentially relevant reports were identified through grey literature searching. Of the 34 potentially relevant reports, 21 did not meet the inclusion criteria. Thirteen reports were included in this review. The study selection process is outlined in a PRISMA flowchart (Appendix 1). One systematic review, three RCTs, two analyses of RCTs, two retrospective cohort studies, one prospective observational study, and four evidence-based guidelines met inclusion criteria. No economic evaluations were identified.

Summary of Study Characteristics

Details on study characteristics, critical appraisal and findings can be found in Appendices 2, 3 and 4, respectively.

Country of origin

The systematic review was performed by a group in Spain and included RCTs from multiple different countries.¹⁶ Three included studies came from North America,¹⁷⁻¹⁹ two studies came from Germany,^{20,21} and one study came from each of New Zealand,²² the UK,²³ and the Netherlands.²⁴ Three of the guidelines were from the UK²⁵⁻²⁷ and one was from Canada.²⁸

Study design

Two RCTs,^{17,18} and two analyses of the same RCT^{22,23} regarding the use of denosumab or zoledronic acid after oral bisphosphonate use were included. One analysis²² examined outcomes after the first administration of study drugs, while the other analysis²³ focused on outcomes at 3 years. Four guidelines were included.²⁵⁻²⁸ One systematic review,¹⁶ one open-label RCT,¹⁹ two retrospective cohort studies,^{20,24} and one prospective observational study²¹ regarding compliance rates were included.

Patient population

All studies included adult women diagnosed with postmenopausal osteoporosis with an overall age ranging from 45 to 89 years old. Of the double-blind RCTs, three studies¹⁷⁻¹⁹ defined osteoporosis as having a BMD T-score below -2.0 and two studies^{22,23} defined osteoporosis as having a BMD T-score below -2.5 without existing vertebral fractures or below -1.5 with moderate vertebral fractures. Two guidelines^{26,27} provided recommendations for postmenopausal women with a BMD T-score below -2.5, one guideline²⁸ focused on men and women over age 50, and another guideline²⁵ was based on one RCT that included postmenopausal women with BMD T-scores between -2.5 and -4.0 at the lumbar spine, total hip, or both locations.

Interventions and comparators

One study¹⁷ examined the use of subcutaneous denosumab after oral alendronate compared to continuing on alendronate therapy while another study¹⁸ examined the use of intravenous zoledronic acid after alendronate. Two studies were post-hoc analyses of the same RCT that compared the use of zoledronic acid to placebo, with subgroup analyses of patients previously treated with bisphosphonates.^{22,23} No criteria for switching treatment were provided, so it is uncertain whether they had continued to decline or were intolerant of bisphosphonate treatment.^{22,23} Of the compliance studies, one study¹⁹ examined the use of denosumab after alendronate or vice versa, while the remaining studies^{16,20,21,24} focused on the use of daily and weekly oral bisphosphonates.

Outcomes measured

Of the studies that examined the use of denosumab or zoledronic acid after oral bisphosphonate use, the main outcomes included percent change in BMD score in the hip, lumbar spine and femoral neck from baseline, and adverse events.^{17,18,22,23} Four of five compliance studies reported compliance as a medication possession ratio (MPR), which is quantified as the number of days of medication supplied within the refill interval divided by the number of days in the refill interval, giving a measure of the extent to which the patient followed the dosing regimen.^{16,20,21,24} Four of five compliance studies also reported on persistence, which is defined as the length of time a patient continues to take his or her medication as prescribed until a prolonged or unacceptable treatment gap is encountered, often ending in discontinuation of the medication.^{16,19-21} Two studies also examined the effect of compliance on fracture risk.^{16,20}

Summary of Critical Appraisal

The systematic review¹⁶ was based on a comprehensive literature search and a summary of characteristics of included studies was provided in addition to an investigation of publication bias, but a list of excluded studies was not provided and it was unclear whether grey literature was included in the search strategy.

Three RCTs and two post-hoc analyses of one RCT were included in the review. Of these, the RCT that the post-hoc analyses were based on described an adequate method of randomization,^{22,23} while the other three did not describe the randomization method.¹⁷⁻¹⁹ Both patient and outcome assessors were blinded in all trials except one open-label trial.¹⁹ All studies performed a power calculation to determine an adequate sample size for detecting clinically significant differences.^{17-19,22,23}

Two retrospective cohort studies and one prospective observational study were identified.^{20,21,24} All of these studies included a large number of patients, with both retrospective studies^{20,24} reflecting current practice. Patient allocation in the prospective observational study was based on investigator judgment and may not be reflective of current practice.²¹

All of the included guidelines had a clear objective, scope, and target population and were developed by appropriate professional groups using clear methodology.²⁵⁻²⁸ All recommendations were derived directly from the evidence that supported them. One guideline²⁸ provided a grade for the included recommendations. Patients' views and cost implications of applying the recommendations were considered in three guidelines.²⁵⁻²⁷ Potential barriers of applying the recommendations were not considered in any of the included guidelines.

Summary of Findings

Efficacy and safety of denosumab (Prolia) after bisphosphonate use

One RCT evaluated the effects of transitioning from weekly oral alendronate to subcutaneous denosumab therapy every six months.¹⁷ This study found that patients transitioned to denosumab had a significantly greater BMD increase in total hip, lumbar spine, femoral neck, and 1/3 radius at the end of 12 months than patients who continued taking alendronate. Among patients who were transitioned to denosumab, larger BMD increases were seen in patients who had a shorter duration of prior alendronate therapy. The safety profile was similar in both treatment groups with regards to adverse events and serious adverse events.

Efficacy and safety of zoledronic acid (Aclasta) after bisphosphonate use

One RCT examined the effects of transitioning from weekly oral alendronate to yearly intravenous (IV) zoledronic acid.¹⁸ This study found no statistically significant difference in lumbar spine BMD increase at the end of 12 months between patients transitioned to zoledronic acid and patients who remained on alendronate. Although the alendronate group exhibited a slightly greater lumbar spine BMD increase than the zoledronic acid group, the criteria for non-inferiority was met. Both treatment groups reported a similar percentage of adverse events and serious adverse events, and the majority of patients preferred zoledronic acid over alendronate therapy.

Two post-hoc analyses^{22,23} of the HORIZON-Pivotal Fracture Trial examined the safety and efficacy of yearly IV zoledronic acid compared to placebo. In both studies, efficacy and safety results were analyzed according to baseline characteristics, one of which was whether or not the patient was a previous bisphosphonate user. One study found that adverse events within 3 days after the first infusion (acute phase responses) was less common in previous bisphosphonate users.²² The other analysis found that zoledronic acid treatment reduced the risk of hip and nonvertebral fractures at 3 years compared to placebo in all subgroups except for previous bisphosphonate users.²³

Compliance rates of women taking denosumab and bisphosphonates

One open-label RCT examined compliance and persistence of women taking oral alendronate weekly compared to subcutaneous denosumab once every 6 months, with therapies crossing over after one year.¹⁹ At the end of the first year, significantly more patients had better compliance with denosumab than alendronate, and this difference was increased after crossover at the end of the second year. Similar results were seen for persistence rates.

Two retrospective cohort studies^{20,24} and one prospective observational study²¹ examined compliance and persistence of bisphosphonate users. One retrospective study found that compliance and persistence with oral bisphosphonates in German women with osteoporosis were inadequate, with persistence rates improving from daily to weekly to monthly regimens. Another retrospective study used hospitalization data from a database of residents of the Netherlands and found that postmenopausal women taking bisphosphonates had an increased odds of non-compliance if started on a daily regimen compared to a weekly regimen, if using greater than 10 different co-medications, or if they required the use of new intestinal agents within the year after starting bisphosphonate therapy.²⁴ The prospective study compared compliance and persistence of various bisphosphonate therapies and found greater compliance

in patients taking once daily medications compared to once weekly medications.²¹ This study also found that younger patients, patients who were aware of the health complications of osteoporosis, and those who were satisfied with the treatment and experienced improvements in quality of life had better compliance and a lower risk of treatment discontinuation.²¹ With regards to treatment compliance and risk of fracture, one systematic review¹⁶ and one retrospective study²⁰ found that the risk of fracture was higher in poorly compliant patients compared to highly compliant patients. The systematic review found that the increased probability of fracture in poorly compliant patients differed at specific sites, with vertebral fractures having the highest risk, followed by hip and nonvertebral fractures.¹⁶

No studies regarding compliance with annual injections of zoledronic acid treatment were identified.

Evidence-based guidelines

Four guidelines provided recommendations on treatments for patients with postmenopausal osteoporosis who have discontinued oral bisphosphonates.²⁵⁻²⁸

The National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance (2010) recommends that denosumab be used in the “primary or secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.” (p. 4)²⁵

Another NICE technology appraisal guidance (2008) recommends strontium ranelate as an alternative treatment option for the “primary prevention of osteoporotic fragility fractures in postmenopausal women who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate.” (p. 6)²⁶ With regards to secondary prevention, a separate NICE guidance recommends strontium ranelate as an alternative treatment option for the “secondary prevention of osteoporotic fragility fractures in postmenopausal women who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate.” (p. 6)²⁷ Intolerance was defined as persistent upper gastrointestinal disturbance that is severe enough to warrant discontinuation of treatment despite following treatment instructions correctly.

The Canadian Medical Association’s clinical practice guidelines for the diagnosis and management of osteoporosis in Canada (2010) recommends, for menopausal women requiring treatment of osteoporosis, that alendronate, risedronate, zoledronic acid, or denosumab be used as first-line therapy for prevention of hip, nonvertebral and vertebral fractures (grade A recommendation; based on systematic reviews/meta-analyses of RCTs or individual well-powered RCTs).²⁸ For postmenopausal women intolerant of first-line therapies, calcitonin or etidronate can be considered for prevention of vertebral fractures (grade B recommendation, based on systematic reviews/meta-analyses of lower quality RCTs or individual lower quality RCTs).

Cost effectiveness

No evidence on the cost effectiveness of using denosumab or zoledronic acid for patients with postmenopausal osteoporosis who have discontinued oral bisphosphonates or are experiencing further decline while on treatment with oral bisphosphonates was identified.

Limitations

In the studies focusing the use of denosumab or zoledronic acid after oral bisphosphonate use, the patients that were enrolled were not necessarily intolerant to bisphosphonates or experienced further decline while taking bisphosphonates, limiting the applicability of the results to the populations of interest. There were also few studies looking at either denosumab (n = 1) or zoledronic acid (n = 3) post-bisphosphonate therapy, limiting the generalizability of the results. The patient population included in each study varied in terms of BMD T-scores and age, which may influence the results and limit comparability. In the studies focusing on compliance rates, these rates may be higher in clinical trials than in real life settings, thereby making the retrospective studies potentially more relevant than the prospective studies. In addition, some compliance studies used non-Canadian samples, potentially limiting the generalizability to the Canadian population. Strontium ranelate is only approved for use outside of North America,¹⁰ limiting the applicability of the recommendations. No evidence on the cost effectiveness of using denosumab or zoledronic acid for patients who discontinued oral bisphosphonates was identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In a head-to-head comparison trial, the use of denosumab in postmenopausal women after alendronate therapy was found to significantly improve BMD compared to those who continued on alendronate. In a separate trial of zoledronic acid use after alendronate therapy, BMD improved to a similar extent as patients continuing on alendronate. Post-hoc subgroup analyses of a placebo-controlled trial found that the use of zoledronic acid was slightly less effective in patients who were on previous bisphosphonate therapy when compared to other subgroups. The authors suggested this may be due to residual bisphosphonate activity, however residual activity of previous treatment is a consideration in all included studies. Patients previously on bisphosphonates experienced fewer adverse events within 3 days of zoledronic acid infusion, suggesting that previous bisphosphonate use is somewhat protective.

The compliance rate of postmenopausal women to oral bisphosphonate therapy was found to be inadequate, with daily regimens showing greater non-compliance than weekly or monthly regimens. Increased non-compliance to bisphosphonate therapy was associated with an increased risk of fracture. Patient compliance and persistence was significantly improved with denosumab once every 6 months compared to alendronate once-weekly. Patient satisfaction and patient knowledge of osteoporosis and treatments all influenced the rate of compliance, emphasizing the importance of individualizing therapy and proper education.

Guidelines suggest that denosumab, zoledronic acid, strontium ranelate, or calcitonin be used in postmenopausal women who are intolerant to oral bisphosphonate therapies such as alendronate, risedronate, or etidronate. As strontium ranelate has not currently been approved for use in North America, this is not currently an option in Canadian settings.

No evidence was identified regarding the cost effectiveness of denosumab or zoledronic acid for the treatment of postmenopausal osteoporosis in patients who have discontinued oral bisphosphonates.

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health

Tel: 1-866-898-8439

www.cadth.ca

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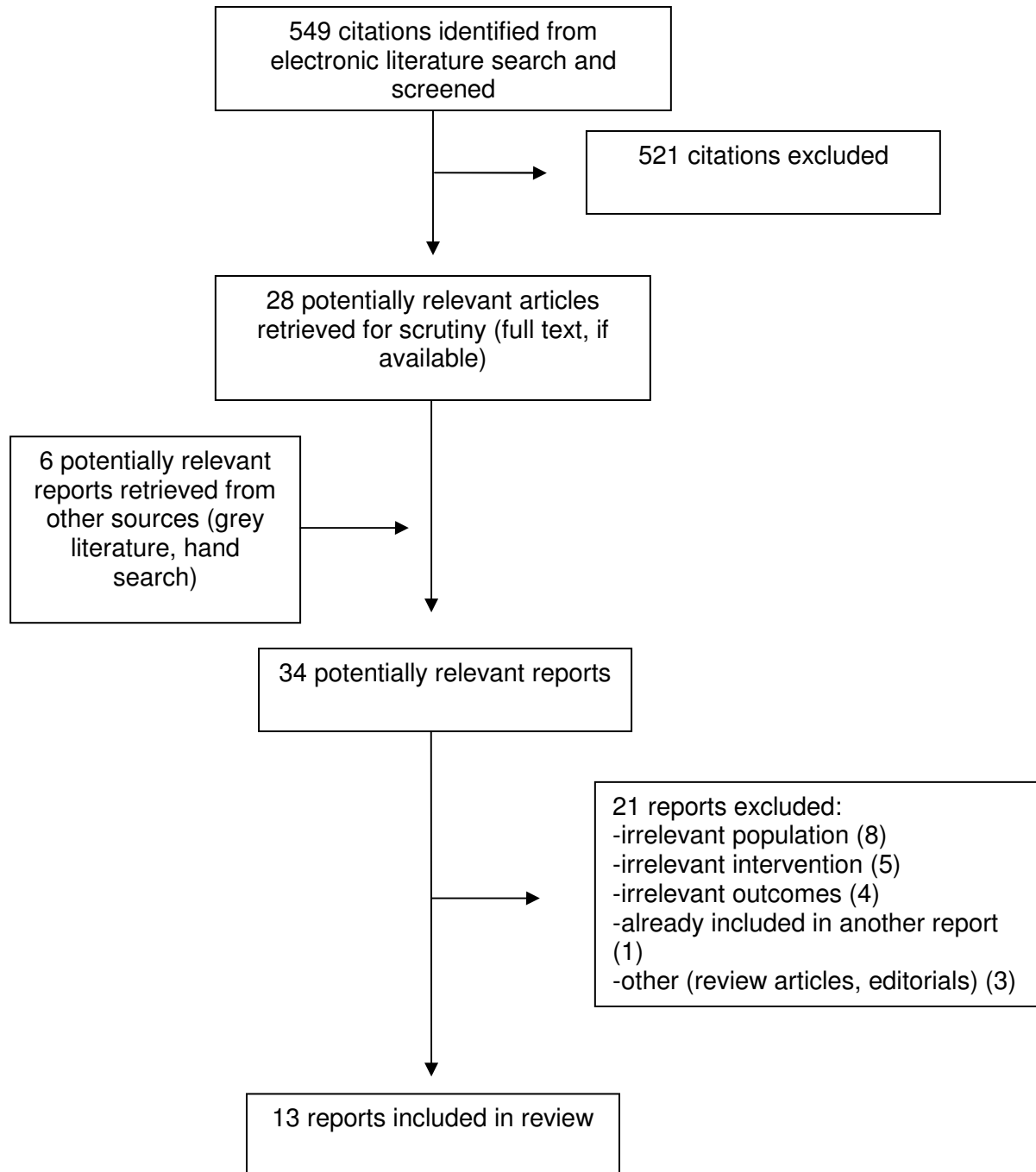
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Imaz ¹⁶ 2010 Spain	Systematic review	15 observational studies including 704,134 patients undergoing bisphosphonate treatment for osteoporosis	Bisphosphonates alone Or Bisphosphonates in combination with other anti-osteoporosis medications		Persistence, compliance (MPR), influence of low compliance on fracture risk
Freemantle ¹⁹ 2012 North America	Open-label, multicenter, crossover RCT 2 years	250 postmenopausal women ≥55 years old with a BMD T-score of ≤ -2.0 and ≥ -4.0 at the lumbar spine, total hip, or femoral neck	Year 1: 70 mg oral alendronate once-weekly Year 2: 60 mg subcutaneous denosumab once every 6 months (n=125)	Year 1: 60 mg subcutaneous denosumab once every 6 months Year 2: 70 mg oral alendronate once-weekly (n=125)	Adherence (compliance and persistence with therapy)
Kendler ¹⁷ 2010 Canada	Double-blind, double-dummy RCT 1 year	504 postmenopausal women ≥55 years old with a BMD T-score of ≤ -2.0 and ≥ -4.0 receiving 70 mg once-weekly alendronate therapy for ≥6 months	60 mg subcutaneous denosumab once every 6 months (n=253)	70 mg oral alendronate once-weekly (n=253)	Percent change in total hip BMD and lumbar spine BMD from baseline to 12 months, adverse events
Reid ²² 2010 New Zealand	Analysis of double-blind, placebo-controlled RCT (HORIZON-Pivotal Fracture Trial) 3 years	7765 postmenopausal women 65-89 years old with a BMD T-score of ≤ -2.5 without evidence of an existing vertebral fracture or ≤ -1.5 with evidence of moderate vertebral fractures	5 mg IV zoledronic acid once-yearly (n=3889) 1000-1500 mg/day calcium and 400-1200 IU/day vitamin D	Placebo (n=3876) 1000-1500 mg/day calcium and 400-1200 IU/day vitamin D	Acute-phase response (adverse events occurring within 3 days of zoledronic acid infusion)
Eastell ²³ 2009 UK	Post-hoc analysis of double-blind, placebo-controlled RCT (HORIZON-Pivotal Fracture Trial) 3 years	7765 postmenopausal women 65-89 years old with a BMD T-score of ≤ -2.5 without evidence of an existing vertebral fracture or ≤ -1.5 with evidence of moderate vertebral fractures	5 mg IV zoledronic acid once-yearly (n=3889) 1000-1500 mg/day calcium and 400-1200 IU/day vitamin D	Placebo (n=3876) 1000-1500 mg/day calcium and 400-1200 IU/day vitamin D	Hip fractures, nonvertebral fractures, change in femoral neck BMD
McClung ¹⁸ 2007 USA	Double-blind, dummy-dummy RCT 1 year	225 postmenopausal women 45-79 years old with a BMD T-score of ≤ -2.0 prior to receiving alendronate therapy for ≥1 year	5 mg IV zoledronic acid infusion once (n=113) 1000 mg/day calcium and 400 IU/day vitamin D	70 mg oral alendronate once-weekly (n=112) 1000 mg/day calcium and 400 IU/day vitamin D	Percent change in lumbar spine BMD from baseline to 12 months, adverse events, patient preference

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Hadji ²⁰ 2012 Germany	Retrospective cohort study	4147 women diagnosed with osteoporosis who had a first prescription of oral bisphosphonates between Dec 2004-Nov 2007	Oral bisphosphonate drugs <u>Daily (n=139)</u> : 10 mg alendronic acid, clodronic acid, etidronic acid, 5 mg risedronate, tiludronic acid <u>Weekly (n=3824)</u> : 35 mg risedronate sodium, 70 mg alendronic acid, <u>Monthly (n=184)</u> : 150 mg ibandronic acid		Compliance, persistence, incidence of fractures
Penning-van Beest ²⁴ 2008 The Netherlands	Retrospective cohort study	8822 women diagnosed with postmenopausal osteoporosis ≥45 years old ≥1 year after starting bisphosphonate therapy	Daily bisphosphonates (n=1639) Daily bisphosphonates that could switch to weekly bisphosphonates within the first year (n=2583) Weekly bisphosphonates (n=4600)		Compliance (MPR) at 3, 6, and 12 months after start of treatment
Ringe ²¹ 2007 Germany	Prospective, multicenter, observational study 1 year	5198 postmenopausal women ≥60 years old with increased risk of osteoporotic fractures according to treating physician	60 mg/daily raloxifene (n=3490) 10 mg/daily alendronate (n=452) 70 mg/weekly alendronate (n=769) 5 mg/daily risedronate (n=487)		Compliance, persistence

BMD=bone mineral density; IV=intravenous; MPR=medication possession ratio; RCT=randomized controlled trial

APPENDIX 3: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Systematic reviews		
Imaz ¹⁶ 2010	<ul style="list-style-type: none"> • Comprehensive literature search based on pre-defined criteria • Summary of study characteristics provided • Risk of publication bias investigated with a funnel plot 	<ul style="list-style-type: none"> • Unclear whether there was duplicate study selection and data extraction • Unclear whether grey literature was included • List of excluded studies not provided
Randomized controlled trials or analysis of RCT		
Freemantle ¹⁹ 2012	<ul style="list-style-type: none"> • Description of losses to follow-up • Power calculation was performed to determine sample size • All patients received assigned treatment 	<ul style="list-style-type: none"> • Method of randomization not described • Patients and outcome assessors not blinded
Kendler ¹⁷ 2010	<ul style="list-style-type: none"> • Patients and outcome assessors blinded • Power calculation was performed to determine sample size • All patients received assigned treatment • Description of losses to follow-up 	<ul style="list-style-type: none"> • Method of randomization not described • Compliance with intervention based on counting of study drug, which may not be reliable methods
Reid ²² 2010	<ul style="list-style-type: none"> • Method of randomization described • Patients and outcome assessors blinded • Power calculation was performed to determine sample size • All patients received assigned treatment 	<ul style="list-style-type: none"> • No description of losses to follow up
Eastell ²³ 2009	<ul style="list-style-type: none"> • Method of randomization described • Patients and outcome assessors blinded • Power calculation was performed to determine sample size • All patients received assigned treatment 	<ul style="list-style-type: none"> • No description of losses to follow up
McClung ¹⁸ 2007	<ul style="list-style-type: none"> • Patients and outcome assessors blinded • Power calculation was performed to determine sample size • All patients received assigned treatment • Description of losses to follow-up 	<ul style="list-style-type: none"> • Method of randomization not described
Non-randomized studies		
Hadji ²⁰ 2012	<ul style="list-style-type: none"> • Large sample size, reflecting current practice • Interventions and outcome measures clearly described 	<ul style="list-style-type: none"> • No randomization or blinding • Retrospective study • Sample may not represent the Canadian population (focus on German population)
Penning-van Beest ²⁴ 2008	<ul style="list-style-type: none"> • Large sample size, reflecting current practice • Outcome measures clearly described 	<ul style="list-style-type: none"> • No randomization or blinding • Retrospective study • Sample may not represent the Canadian population (focus on Dutch population) • Compliance (outcome) based on dispensing data, which may be inaccurate
Ringe ²¹ 2007	<ul style="list-style-type: none"> • Large sample size • Prospective study • Sample taken from multiple countries and is representative of population of interest • Interventions and outcome measures clearly described 	<ul style="list-style-type: none"> • No randomization or blinding • Patient allocation to treatment groups may not be reflective of current practice • Patients not equally distributed between treatment groups • Patient baseline characteristics different between treatment groups

First Author, Publication Year	Strengths	Limitations
Guidelines		
National Institute for Health and Clinical Excellence ²⁵ 2010	<ul style="list-style-type: none"> • Clearly defined objectives, scope and target populations • Guideline development group included individuals from relevant professional groups and patient representation • Guideline development methodology described • Recommendations are directly linked to evidence • Cost implications of applying the recommendations were considered 	<ul style="list-style-type: none"> • Potential barriers of applying the recommendations not considered
Canadian Medical Association ²⁸ 2010	<ul style="list-style-type: none"> • Clearly defined objectives, scope and target populations • Guideline development group included individuals from relevant professional groups • Guideline development methodology described • Recommendations are directly linked to evidence 	<ul style="list-style-type: none"> • Patients' views and preferences were not directly sought • Potential barriers of applying the recommendations not considered • Cost implications of applying the recommendations not considered
National Institute for Health and Clinical Excellence ^{26,27} 2008	<ul style="list-style-type: none"> • Clearly defined objectives, scope and target populations • Guideline development group included individuals from relevant professional groups and patient representation • Guideline development methodology described • Recommendations are directly linked to evidence • Cost implications of applying the recommendations were considered 	<ul style="list-style-type: none"> • Potential barriers of applying the recommendations not considered

APPENDIX 4: Summary of Findings

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Systematic reviews		
Imaz ¹⁶ 2010	<p>Data from five studies (n=236,540, followed for one year) were pooled to provide a persistence mean of 184.09 days (range 98-243 days). Data from another five studies (n=234,737, followed for one year) was pooled to calculate a MPR mean of 66.93% (range 54.6-81.3%).</p> <p>Fracture risk between poorly and highly compliant patients was analyzed in six studies (n=171,063) and was found to be 1.46 (95% CI 1.34-1.60). The probability of fracture was 46% higher in poorly than highly compliant patients. The increased probability of fracture for specific sites is as follows: nonvertebral, 16%; hip, 28%; clinical vertebral, 43%.</p>	<p>"Our results demonstrate the early occurrence of nonadherence to bisphosphonate therapy. One-third of the patients included in our review were non-compliant within 1 year of treatment initiation. Half the patients stopped purchasing the drug 184 days after starting treatment...Although we found that poor bisphosphonate compliance increases fracture risk, a dose-effect relationship was not verified, perhaps because the limited number of studies pooled." (p. 1949)</p>
Randomized controlled trials or analysis of RCT		
Freemantle ¹⁹ 2012	<p>At the end of the first year, 11.9% were non-adherent to denosumab and 23.4% were non-adherent to alendronate (absolute difference 10.5%, 95% CI 1.3%-19.7%; rate ratio 0.54, 95% CI 0.31-0.93, p=0.026). After cross-over, 7.5% were non-adherent to denosumab and 36.5% were non-adherent to alendronate (absolute difference 30.9%, 95% CI 20.6%-41.3%; rate ratio 0.20, 95% CI 0.10-0.41, p<0.001).</p> <p>In the first year, non-persistence was 9.5% for denosumab and 20.2% for alendronate (absolute difference 9.8%, 95% CI 1.1%-18.5%; rate ratio 0.50, 95% CI 0.27-0.93, p=0.029). After crossover, non-persistence was 6.6% for denosumab and 32.2% for alendronate (absolute difference 27.7%, 95% CI 17.6%-37.7%; rate ratio 0.20, 95% CI 0.09-0.43, p<0.001).</p>	<p>"In this study, postmenopausal women who received subcutaneous injections of denosumab every 6 months had significantly better adherence, compliance, and persistence than women who self-administered alendronate orally once weekly." (p. 323)</p>
Kendler ¹⁷ 2010	<p>At month 12, total hip BMD increased by 1.90% (95% CI 1.61%-2.18%) in subjects transitioned to denosumab compared with a 1.05% increase (95% CI 0.76%-1.34%) in subjects continuing on alendronate therapy. Lumbar spine BMD increased by 3.03% (95% CI 2.63%-3.44%) in the denosumab group compared with 1.85% (95% CI 1.44%-2.26%) in the alendronate group. The increase in BMD with denosumab versus alendronate was statistically significant (p<0.0001). Significant increases in BMD were also seen at the femoral neck and 1/3 radius (p<0.0121)</p> <p>At the total hip, there was a larger BMD increase with denosumab among subjects who had a shorter duration of prior alendronate therapy.</p>	<p>"In this trial in postmenopausal women with low BMD who were previously taking alendronate, transitioning to denosumab was found to increase BMD and reduce markers of bone turnover to a greater extent than continued alendronate therapy with no clinical hypocalcemic events and a similar adverse-event profile. Notably, denosumab treatment resulted in significantly greater gains in BMD than continued alendronate treatment at all skeletal sites evaluated." (p. 78)</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<p>There were a similar number of subjects in each treatment group reporting adverse events during the study (78% denosumab, 79% alendronate). Serious adverse events were reported in 5.9% of denosumab-treated subjects and 6.4% of alendronate-treated subjects. One subject died in the denosumab group, but this was considered unrelated to study treatment.</p>	
Reid ²² 2010	<p>The incidence of acute-phase responses were less common in previous bisphosphonate users (OR 0.78, 95% CI 0.66-0.92, P=0.0005)</p>	<p>"It does confirm that previous bisphosphonate use (almost always oral) is protective but only partly so. Thus, subjects randomized to zoledronic acid who have previously used these drugs still experience an APR in 32% of cases, as opposed to 44% of those who were bisphosphonate naïve." (p. 4386)</p>
Eastell ²³ 2009	<p>Zoledronic acid treatment was associated with significant reductions in the risk of vertebral fractures at 3 years in all subgroup categories compared with placebo, including previous bisphosphonate users (4.2% vs 10.9%, P<0.001). Zoledronic acid treatment reduced the risk of hip fracture and nonvertebral fracture over 3 years across all subgroups (hazard ratio <1) compared to placebo except for those treated previously with bisphosphonates (hip fracture 2.1% vs 1.4%, P=0.38; nonvertebral fracture 9.6% vs 9.0%, P=0.71).</p>	<p>"The interactions between risk factors and treatment were not significant for nonvertebral fracture or hip fracture. For both, there was a weak relationship with prior use of bisphosphonates. We appreciate that bisphosphonates such as alendronate may continue to suppress bone turnover and possibly fracture risk for several years after stopping them, and this might mean that the effect of a newly introduced treatment might be less effective." (p. 3223)</p>
McClung ¹⁸ 2007	<p>At month 12, total lumbar spine BMD increased by 0.120% (SE=0.273) in the zoledronic acid group and 0.828% (SE=0.288) in the alendronate group compared to baseline. There was no statistically significant difference between the treatment groups, and the non-inferiority margin was met.</p> <p>There were a similar percentage of patients in each treatment group reporting adverse events during the study (86.7% zoledronic acid, 80.4% alendronate). Serious adverse events were reported in 12 patients in the zoledronic acid group and 11 patients in the alendronate group.</p> <p>Of the 221 patients who responded to the questionnaire, once-a-year zoledronic acid infusion was preferred by 78.7% compared to 9% for alendronate.</p>	<p>"Patients can be safely switched from oral alendronate to an infusion of 5 mg zoledronic acid with maintenance of therapeutic effect for at least 12 months. A once yearly IV infusion may be preferable to patients and ensures adherence over 12 months." (p. 128)</p>
Non-randomized studies		
Hadji ²⁰ 2012	<p>Persistence rate after 12 months: 27.9%</p> <ul style="list-style-type: none"> - Daily regimen: 7.2% - Weekly regimen: 28.6% - Monthly regimen: 29.4% <p>Persistence rate after 2 years: 12.9%</p> <p>Of patients with at least two oral bisphosphonate prescriptions in the period of</p>	<p>"The overall persistence with oral bisphosphonates in the present analysis can be considered unsatisfactory with regard to clinical treatment targets. Consistent with the persistence findings, compliance (measured as MPR) was poor: more than 33% of the patients showed poor or very poor compliance (MPR <80%) with oral</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<p>persistence (n=3188):</p> <ul style="list-style-type: none"> - MPR\geq80 (good compliance): 66.3% - MPR<80 (poor compliance): 33.7% <p>Relative number of patients without fracture from 3 months after start of treatment onwards:</p> <ul style="list-style-type: none"> - Compliant patients: 88.1% - Non-compliant patients: 85.0% <p>Reduction in fracture risk:</p> <ul style="list-style-type: none"> - Compliant vs non-compliant: 26.6% - Compliant and persistent: 37.7% - Compliant but not persistent: 19.9% : 	<p>bisphosphonate treatment. The regression analyses indicated that good compliance can significantly reduce fracture risk, with a hazard ratio of 0.734 for compliant patients compared with those who were not compliant." (p. 228)</p>
<p>Penning-van Beest²⁴ 2008</p>	<p>Noncompliant (MPR<50%) bisphosphonate users who started on a daily regimen</p> <ul style="list-style-type: none"> - 3 months : 23% - 1 year : 41% <p>Noncompliant (MPR<50%) bisphosphonate users who started on a weekly regimen</p> <ul style="list-style-type: none"> - 3 months : 14% - 1 year : 24% <p>Determinants of 1-year non-compliance with bisphosphonates were identified by comparing 2720 (31%) non-compliant women to 5079 (58%) compliant women (MPR\geq80%)</p> <ul style="list-style-type: none"> - Starting on daily dosing regimen: OR 2.31 (95% CI 2.04-2.62) - Using >10 different co-medications prior to bisphosphonates: OR 1.87 (95% CI 1.41-2.49) - New use of intestinal agents in year after starting bisphosphonates: OR 1.22 (95% CI 1.09-1.36) 	<p>"Although women starting on a weekly dosing regimen were more compliant with bisphosphonates compared to women starting on a daily regimen, compliance rates were still low...Initial daily dosing, number of different co-medications used and new use of intestinal agents in the year after starting bisphosphonate treatment were associated with a 1.2 to 1.9 times increased odds of non-compliance." (p. 1341-1342)</p>
<p>Ringe²¹ 2007</p>	<p>High therapy compliance (\geq80%):</p> <ul style="list-style-type: none"> - Raloxifene: 80% - Daily Alendronate: 79% - Risedronate: 76% - Weekly Alendronate: 65% <p>Treatment discontinuation:</p> <ul style="list-style-type: none"> - Raloxifene: 18% - Daily Alendronate: 17% - Risedronate: 21% - Weekly Alendronate: 26% <p>Risk of early discontinuation:</p> <ul style="list-style-type: none"> - Surgical menopause: OR 1.44 (95% CI 1.17-1.77) - Thin frame as primary reason for therapy: OR 1.23 (95% CI 1.05-1.45) - Patients' lack of knowledge that osteoporosis can be prevented by medications: OR 1.35 (95% CI 1.13-1.61) - Age: OR 1.02 per year (95% CI 1.13-1.61) 	<p>"The results of this study demonstrate that there is a similar level of compliance and non-persistence among daily oral treatments of osteoporosis with the discontinuation rates of the daily alendronate, risedronate and raloxifene therapies after 1 year of treatment ranging between 18% to 22%...Greater compliance was seen in patients taking once daily medications, when compared to patients taking once weekly medication. Younger patients, those with awareness of health complications of osteoporosis, those who were satisfied with the treatment and who experienced an improved quality of life also had better compliance and lower treatment discontinuation." (p. 2684, 2686)</p>

BMD=bone mineral density; CI=confidence interval; OR=odds ratio; MPR=medication possession ratio; SE=standard error