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Duration of Bisphosphonate Treatment for Patients with Osteoporosis: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

ACP	American College of Physicians
AE	adverse event
AFF	atypical femoral fractures
AGREE II	Appraisal of Guidelines for Research and Evaluation Instrument II
AHRQ	Agency for Healthcare Research and Quality
ALN	alendronate
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
AR	absolute risk
BIOSIS	BioSciences Information Service of Biological Abstracts
BIS	bisphosphonate
BMD	bone mineral density
CGC	clinical guidelines committee
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CRD	University of York Centre for Reviews and Dissemination
DXA	dual-energy x-ray absorptiometry
EMAS	European Menopause and Andropause Society
EMBASE	Excerpta Medica database
ETN	etidronate
FLEX	Fracture Interventional Trial Long Term Extension
FRAX	tool to evaluate fracture risk of patients
GP	general practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HORIZON-PFT	Health Outcomes and Reduced Incidence with Zoledronate One Yearly – Pivotal Fracture Trial
HR	hazard ratio
HRQoL	health related quality of life
HTA	health technology assessment
IBN	ibandronate
MA	meta-analysis
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Heading
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NIH	National Institutes of Health
NMA	network meta-analysis
NOGG	National Osteoporosis Guideline Group
NR	not reported
NRS	non-randomized study
OCEBM	Oxford Centre for Evidence-Based Medicine
ONJ	osteonecrosis of the jaw
OR	odds ratio
PM	postmenopausal
PROSPERO	International prospective register of systematic reviews
PubMed	public MEDLINE
RACGP	Royal Australian College of General Practitioners
RCT	randomized controlled trial
RR	relative risk
RSN	risedronate
SD	standard deviation
SEIOMM	Spanish Society for Research on Bone and Mineral Metabolism
SR	systematic review
WHO	World Health Organisation
WRHA	Winnipeg Regional Health Authority
ZLN	zoledronic acid

Context and Policy Issues

Throughout life bone tissue is constantly formed and resorbed; however, with age this process becomes less effective. Osteoporosis is a bone disease characterised by a deterioration of bone tissue in which bones become progressively less dense and more fragile.[1] When bones are severely weakened by osteoporosis they can fracture easily as a result of minimal trauma (such as falling from standing).[2] Despite overall skeletal fragility, fractures of the wrist, shoulder, vertebrae and hip are those most commonly associated with osteoporosis.[1,2]

Osteoporosis can affect Canadians of all ages; though, it is more common in those 50 years or older.[3] In this population, it is estimated there were 57,413 hospitalizations for a total of 832,594 days from April 1, 2007 to March 31, 2008, costing $1.181 billion (2010 Canadian dollars) in emergency care, acute care admissions, and same day surgeries.[4] Furthermore, females are disproportionately affected then males.[1,4] There are many risk factors for osteoporosis, including cigarette smoking, long term use of corticosteroids or other high risk medications, and insufficient dietary intake of calcium and vitamin D.[1,5] The presence of these, along with findings from a physical examination and laboratory investigations, may prompt further investigation with a bone mineral density (BMD) test using a dual X-ray absorptiometry (DXA) method.[6] A DXA t-score result between –1 and –2.5 standard deviations indicates low bone mass (osteopenia), while osteoporosis is a t-score at or below –2.5 standard deviations.[1,3] This report will focus on patients with osteoporosis.

The goals of therapy for patients with osteoporosis include the prevention of fractures, prevention of associated disability and loss of independence, as well as the preservation or enhancement of bone mass.[5] There are several pharmacological treatments for established osteoporosis, such as: bone resorption inhibitors, which slow down bone loss (e.g., bisphosphonates [BIS], denosumab, raloxifene, and estrogen), as well as bone formation agents, which stimulate the formation of bone tissue (e.g., teriparatide).[5] This report will focus on the BIS class of pharmaceuticals, which are the mainstay of osteoporosis treatment and include: alendronate (ALN), etidronate (ETN), risedronate (RSN), and zoledronic acid (ZLN).

As with any drug therapy, there are adverse effects (AE) associated with BISs and their antifracture benefits ought to be weighed against any possible risks to the patient. Because of concerns about serious AEs, such as osteonecrosis of the jaw (ONJ), atrial fibrillation, and atypical femoral fractures (AFF), there have been suggestions of implementing drug holidays as part of the therapy, where the medication is stopped for a period of time, often several years.[3,5,7-12] However, the optimal duration of therapy before a drug holiday could be considered and the length of the drug holiday (either indefinite or otherwise), is uncertain and remains a clinical controversy.

CADTH has previously reviewed the evidence for the use of bisphosphonates.[13-15] One report was a list of abstracts based on evidence available in August of 2019,[15] one focused on a different patient population (patients with osteopenia and low risk fractures),[14] and another focused on prevention of osteoporosis in patients treated with systemic corticosteroids.[13] The objective of the current report is to evaluate the clinical evidence and evidence-based guidelines regarding various treatment durations of BISs for the treatment of osteoporosis.

Research Questions

1. What is the clinical effectiveness of various treatment durations and courses of bisphosphonates for osteoporosis?
2. What are the evidence based guidelines regarding length of treatment with bisphosphonates for osteoporosis?

Key Findings

One relevant health technology assessment and four systematic reviews (including one with meta-analysis) were identified as clinical evidence of various treatment duration and courses of bisphosphonates for osteoporosis.

The identified literature were heterogenous and revealed mixed conclusions regarding optimal treatment duration of bisphosphonates for osteoporosis. Incidence of atypical femoral fractures increased with duration of bisphosphonate treatment. Other types of adverse events were generally no different between the various durations of treatment reported, except for one study reporting four deaths (none considered associated with treatment) in their continuation group compared with none in the discontinuation group. No clear direction emerged regarding the effect of treatment duration on bone mineral density or on risks related to other types of fractures (e.g., vertebral, nonvertebral, morphometric).

Six evidence-based guidelines were identified regarding the length of treatment with bisphosphonates for osteoporosis. These offer no clear direction on optimal duration of bisphosphonate treatment or drug holidays; however, most guidelines are in concordance that regular patient monitoring and the individualisation of treatment in response to clinical and paraclinical manifestations.

The limitations of the included studies, such as the heterogeneity of primary studies included in the systematic reviews and the low-quality evidence upon which guideline recommendations were based, should be considered when interpreting the results.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline via OVID, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were bisphosphonates and osteoporosis. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and August 16, 2019. Internet links were provided, where available.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed

for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients of any age with osteoporosis
Intervention	Q1-2: Bisphosphonate therapy (e.g., alendronate, zoledronic acid) of any dose and of any prescribed length of treatment (e.g., indefinite, specific timeframe [e.g. 5 years only, 10 years only], based on bone mass density readings, drug holidays)
Comparator	Q1: Bisphosphonate therapy (e.g., alendronate, zoledronic acid) of an alternative length of treatment or treatment course (e.g., indefinite, specific timeframe, based on bone mass density readings, drug holidays, stopping treatment after a length of time, stopping treatment and receiving placebo) Q2: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., number of fractures, quality of life, mortality, adverse events) Q2: Evidence based guidelines on recommended length of treatment of bisphosphates
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in **Table 1** or they were duplicate publications. SRs that had broader inclusion criteria than the present review were examined in detail to ascertain whether data could be extracted from a relevant sub-set of included studies, rather than excluding the SR entirely. Primary studies that had a mixed population at baseline (i.e., some participants with osteopenia and others with osteoporosis) were only included if authors reported relevant results stratified by initial bone mineral density (BMD) t-score or baseline diagnosis. Primary studies retrieved by the search were excluded if they were captured in one or more included SR. Primary studies that were reported in multiple SRs are noted as such, and results were extracted from the publication reporting the most complete data.

Critical Appraisal of Individual Studies

The included Health Technology Assessment (HTA) and SRs were critically appraised by one reviewer using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2),[16] and the guidelines were assessed with the Appraisal of Guidelines for Research Evaluation II (AGREE II) instrument.[17] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 196 citations were identified in the literature search. Following screening of titles and abstracts, 183 citations were excluded and 13 potentially relevant reports from the electronic search were retrieved for full-text review. In addition, 10 potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 23 potentially relevant articles, 12 publications were excluded for various reasons, while 11 publications met the inclusion criteria and were included in this report. These were

comprised of one HTA,[18] four systematic reviews (SR),[19-22] including one with meta-analysis (MA),[20] and six guidelines.[6,23-27]

Appendix 1 presents the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[28] flowchart of the study selection. Note that because the included HTA and SRs had broader inclusion criteria than the present review (i.e., were wider in scope), only subsets of primary studies from the included systematic reviews that met the selection criteria for the present review are described.

Appendix 6 includes seven additional references that did not meet the inclusion criteria of this report but may be of interest.

Summary of Study Characteristics

One HTA,[18] four SRs,[19-22] including one MA,[20] and six guidelines[6,23-27] were identified and included in this review. The HTA,[18] met the inclusion criteria for this report; however, none of the primary studies included in the HTA met the eligibility criteria for this report; therefore, no summary of these primary studies could be provided. Detailed characteristics are available in Appendix 2, Table 2, and Table 3.

Study Design

The HTA,[18] was published in 2016, three SRs were published in 2019,[19-21] and one in 2014.[22] They sought out relevant RCTs,[19-22] clinical trials,[20,21] cohort studies,[21] and observational studies.[19,20] There were nine,[19] five,[20] seven,[21] and four[22] relevant primary studies from these SRs, with some study overlap as shown in Appendix 5 Table 8, resulting in 17 unique primary studies.

Six guidelines were identified regarding osteoporosis that contained recommendations for the duration of BIS treatment.[6,23-27] Four guidelines are published in 2017,[23-26] one in 2015,[27] and one in 2014.[6] The first guideline, by the American College of Physicians (ACP), is an update to a 2011 SR by the Agency for Healthcare Research and Quality (AHRQ).[23] The second, by the European Menopause and Andropause Society (EMAS), is based on a SR of published literature up to 2017.[24] The third, by the National Osteoporosis Guideline Group is based on evidence from published SRs, MAs, and RCTs from a PubMed search.[25] The fourth guideline, by The Royal Australian College of General Practitioners (RACGP), is based on a SR to update their 2010 guidelines.[26] The fifth, published by the Winnipeg Regional Health Authority (WRHA) is based on a SR to update their 2010 guideline.[6] Lastly, while the summary of the sixth guideline, published by the Spanish Society for Research on Bone and Mineral Metabolism (*SEIOMM*), was published in English, the full guideline was in Spanish; therefore, we were not able to extract data on study design.[27]

As indicated in Table 3, guideline authors used a variety of evidence quality assessment methods, including the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool,[23] A Measurement Tool to Assess Systematic Reviews (AMSTAR),[25] the National Health and Medical Research Council (NHMRC) grades of recommendation,[26] and the Oxford Centre for Evidence-Based Medicine (OCEBM) tool.[27] One guideline,[6] used a quality assessment tool developed for the 1998 Canadian clinical practice guidelines for diabetes, while the other did not report performing a quality assessment of the evidence.[24] Recommendations were developed by consensus,[26] a modified Delphi method,[6] or by committee vote,[23,25] Recommendation development methods were unclear in one guideline[24] and it were unable to be assessed in another.[27]

Country of Origin

The HTA[18] and one SR[19] were authored in the United Kingdom. Other SRs were authored in the United States of America[20,21] and Norway.[22]

The guidelines were developed in the United States of America,[23] Greece,[24] the United Kingdom,[25] Australia,[26] Spain,[27] and Canada.[6]

Patient Population

The HTA included studies with women 65 years of age or older or men 75 years of age or older.[18] Two SRs included postmenopausal (PM) women,[19,22] with osteoporosis,[22] or on osteoporosis medication for one year or more,[19] Two SRs included men,[20,21] the first considered men or PM women aged 50 years or older[20], while the second considered participants with osteoporosis or osteopenia who had received osteoporosis treatment for at least three years.[21] The populations of the primary studies included within the SRs were heterogenous, including some studies with only women, only PM women, or mixed sexes; a variety of ages over 50 years; varying baseline characteristics (e.g., number of risk factors, number of fractures, BMD t-score); and varying number of participants up to 188,814.

The target population of the ACP guidelines are adults with low BMD or osteoporosis, with clinicians involved in their care as the intended user.[23] The European, United Kingdom, and Australian guidelines target men 50 years or older and PM women,[24-26] and the intended users are health care professionals involved in osteoporosis management.[25,26] Whereas we were unable to determine the intended user of the Spanish guidelines, their target population are men or PM women diagnosed with osteoporosis.[27] Lastly, the Canadian guidelines target women and men over the age of 50 and are intended for Manitoba health care providers as well as policy makers.[6]

Interventions and Comparators

The HTA evaluated BISs compared to each other, to placebo, or to other non-active treatment.[18] In three SRs, various osteoporosis pharmacotherapies such as BISs (e.g., alendronate [ALN], risedronate [RSN], ibandronate, [IBN], etidronate [ETN], or zoledronic acid [ZLN]) or denosumab, were compared by varying treatment lengths.[19,21,22] The fourth SR compared long-term (i.e. three or more years) osteoporosis drug treatments of any kind to controls (i.e., placebo or active control) or to a drug holiday of one year or more.[20] The interventions and comparators of the included studies were heterogenous and included various BISs (i.e., ALN, RSN, IBN, ETN, and ZLN), for various lengths of time (ranging from one to 10 years) and with various comparators such as placebo or no drug (i.e., a drug holiday).

The guidelines considered a broader scope of osteoporosis treatments, including BISs, and denosumab,[6,23-27] and some also considered teriparatide, selective estrogen receptor modulators, estrogen, calcium, and vitamin D.[6,23,25-27]

Outcomes

The outcomes considered in the HTA included: fragility fractures, BMD at the femoral neck, mortality, adverse events (AE), compliance, health related quality of life (HRQoL), and health care resource use.[18]

The SRs considered outcomes relating to: bone turnover markers,[19] BMD,[19-22] fractures,[19-22] AEs,[20,22] osteonecrosis of the jaw (ONJ),[19] and atypical femoral fractures (AFF).[19,20]

The outcomes of interest in three of the guidelines included: reduction in fractures,[23,24,26] BMD,[26] and AEs[23,24] Outcomes were not specified at the outset in two guidelines,[6,25] and were not able to be assessed in another.[27]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 4, and Table 5.

Health Technology Assessment

The HTA had several strengths, such as: clear objectives and inclusion criteria, reporting of key search terms and search strategies, provision of a list of included studies and summary of their characteristics, and a quality assessment of included studies using an appropriate tool. Assessors registered their protocol to an online database of systematic review protocols on health-related topics (i.e., PROSPERO) prior to the conduct of the review. Furthermore, they considered risk of bias when interpreting and discussing the results of individual studies. Attrition of 10% or greater was found in 63% of included studies, five trials were either open label or single blind and therefore at high risk of performance bias, and 28% of studies reported assessing outcomes in a blinded manner.[18] These strengths of reporting increase confidence in the findings and the reproducibility of the HTA.

Systematic Reviews

Three SRs[19-21] (one with meta-analysis)[20] included clear objectives and inclusion criteria, while one SR did not.[22] Two SRs did not describe included studies in adequate detail, with poor consistency in reporting the population, intervention, comparator, and research design.[19,22] All SRs reported on source of funding for the review.[19-22]

Reporting issues were apparent in one SR[19] where discrepancies were identified between results stated in the SR and those in primary studies. These reporting issues decrease the confidence in the findings and the reproducibility of the Dennison, 2019[19] SR.

One SR reported an a priori protocol registered to an online database of systematic review protocols on health-related topics (i.e., PROSPERO), performing study selection and data extraction in duplicate, [20] while the others did not. A comprehensive literature search strategy, including hand searching of the bibliography of eligible studies, was used in two SRs,[20,21] while the others did not.[19,22]

The quality of included studies was assessed by Fink, 2019[20] using Agency for Healthcare Research and Quality (AHRQ) criteria and by Nayak, 2019[21] using the Cochrane risk of bias tool and the Newcastle-Ottawa quality assessment scale, while other SRs did not perform quality assessments, introducing uncertainty in their results.[19,22]

Furthermore, Fink, 2019[20] inferred fracture risk data from studies not designed to compare fracture incidence between groups. For instance, the primary study by Tonino, 2000[29] and the one by Bone, 2004[30] were designed to measure change in BMD and reported the number of incident fractures as AEs. In addition, their sample size ranged from 247 to 350 participants and it is unclear if they were adequately powered to report on fracture risk. Despite this, authors produced results on between-group relative risk differences of fractures which may lead to incorrect conclusions.

Authors of the SR with MA[21] justified combining the data in a meta-analysis and they used the DerSimonian and Laird random-effect method, to calculate summary effect size

estimates. However, unless all studies are of similar size, the DerSimonian and Laird method is known to be inefficient when estimating the between-study variance, but efficient when estimating treatment effect.[31] The two cohort studies that were part of the MA had 39,502 participants[32] and 183 participants.[33] As such, the meta-analysts were correct in restricting their inference to statements about the treatment effect only. In addition, the degree of inconsistency between the two studies (i.e., heterogeneity) was assessed as 94.3% (I^2 value); yet, authors did not discuss the likely impact on the results.[21]

Evidence-Based Guidelines

In the six guidelines[6,10,23-27] the scope and purpose were well described. While only one guideline is developed in Canada,[6,10] two others are developed in countries part of the Commonwealth of Nations,[25,26] with universal or near-universal health care coverage for core medical services, and their findings may be generalizable to the Canadian health care setting. The integral version of one guideline is only available in Spanish, restricting the assessment of strengths and limitations to information that is published in the English summary[27]

None of the guidelines sought the views and preferences of the target population.[6,10,23-27] All of the guidelines provided an explicit link between the recommendations and the evidence, as well as the criteria for selecting the evidence and the strengths and limitations of the evidence.[6,10,23-27] The methods for formulating recommendations is described in four guidelines,[6,23,25,26] but not in one,[24] and it is unable to be assessed in another.[27] Four guidelines indicate that their recommendations have been externally reviewed by experts prior to publication,[6,23,25,26] while one guideline did not,[24] and it is unable to be assessed in another.[27] Three guidelines provided a procedures for future updates to their recommendations.[23,25,26]

Summary of Findings

A detailed summary of findings and guideline recommendations is provided in Appendix 4, Table 6, and Table 7. The HTA,[18] met the inclusion criteria for this report; however, none of the primary studies included in the HTA met the eligibility criteria for this report; therefore, no summary could be provided.

Clinical Evidence for Varying Treatment Durations and Courses of Bisphosphonates for Osteoporosis

Bone Mineral Density

Information regarding the effect of duration and course of BIS treatment for osteoporosis on BMD was available from four unique primary studies[29,30,33,34] included, with overlap, in three SRs.[19,21,22]

A cohort study[33] in the Dennison, 2019[19] SR reported that “BMD trends were similar in patients who sustained a fracture during the holiday versus those who did not sustain.”[19] (p.1737) (no effect estimates or statistics provided).

Two unique primary studies[29,34] in the Nayak, 2019[21] SR discussed mean percent change in BMD between various timepoints. The first primary study compared ALN 5 mg for seven years versus ALN 10 mg for seven years versus ALN 20 mg for two years, followed by 5 mg for three years, followed by two years of placebo.[29] BMD results measured at the lumbar spine between year six and seven favoured the continuation groups, while those measured at the femoral neck, trochanter, distal third of the forearm, and total body were no

different between groups.[21] In the second study, trialists compared ETN for seven years versus ETN for five years followed by two years of placebo.[34] BMD results measured at the spine favoured the continuation groups at the end of year seven.[21] However, BMD results measured at the femoral neck, were non-statistically significant between the placebo group and the continuation group when measured at the end of year six.[21] Similarly, BMD results measured at the distal radius, were non-statistically significant between the placebo group compared with the continuation group when measured at the end of year six,[21] and again at the end of year seven.[21]

One additional primary study[30] in both the Nayak, 2019[21] SR and Eriksen, 2014[22] SR compared ALN 5 mg for 10 years versus ALN 10 mg for 10 years versus ALN 20 mg for two years followed by ALN 5 mg for three years followed by five years of placebo.[30] Nayak, 2019[21] reported mean BMD percent change between years six to 10 and between years eight to 10. These results measured at the lumbar spine between years six to 10 as well as eight to 10 favoured the continuation groups,[21] while those measured at the femoral neck were unfavourable in the placebo group but non significant in the ALN groups.[21] However, Eriksen, 2014[22] reported mean BMD percent change relative to pre-treatment levels for the lumbar spine, femoral neck, trochanter, and total hip, and results favoured the ALN 10 mg for 10 year group.[22] The results of the placebo group were equal to, or better than, those of the ALN 5 mg for 10 year when looking at measurements of the lumbar spine, trochanter, and total hip.[22]

Antifracture Efficacy

Information regarding the effect of duration and course of BIS treatment for osteoporosis on antifracture efficacy was available from two unique primary studies[8,34] included in one SR.[21]

The first primary study compared ZLN for six years versus ZLN for three years plus three years of placebo.[8] Odds ratio (OR) of fractures at the femoral neck (0.36; 95% CI, 0.15 to 0.77; *P* = 0.01) and hip (0.26; 95% CI, 0.08 to 0.69; *P* = 0.0113) favoured the six year treatment group compared with the placebo group.[21] The second primary study compared ETN for seven years versus ETN for five years plus two years of placebo.[34] The number of morphometric vertebral fracture between the sixth and seventh year of the study favoured the continuation group (2.4%, n = 1/42) over the placebo group (10.2%, n = NR)).[21]

Bone turnover markers

Information regarding the effect of duration and course of BIS treatment for osteoporosis on bone turnover markers was available from one primary study[30] included in the Eriksen, 2014 SR.[22] The primary study compared ALN 5 mg for 10 years versus ALN 10 mg for 10 years versus ALN 20 mg for two years followed by ALN 5 mg for three years followed by five years of placebo.[30] The authors reported that the ALN group (both dose groups combined) maintained a reduction in bone turnover markers, while the placebo group saw a "small increases in [bone turnover marker] levels (including [bone-specific alkaline phosphatase]) that were still below the pretreatment values at the end of the extension period"[22] (*p*.131) (no effect estimates or statistics provided).

AE – Atypical Femoral Fractures

Information regarding the effect of duration and course of BIS treatment for osteoporosis on atypical femoral fractures (AFF) was available from five unique primary studies[35-39] included, with overlap, in two SRs.[19,20]

Three unique primary studies[36,37,39] in the Dennison, 2019[19] SR discussed AFFs. The first was a combined cohort and case-control study of 59 cases of AFF and 263 controls (i.e., ordinary subtrochanteric or shaft fractures) who were also using BISs.[39] Dennison, 2019 reported that the risk of AFF after BIS discontinuation decreased by 70% per year since last use (OR = 0.28; 95% CI, 0.21 to 0.38).[19] The second study was a cohort of 188,814 individuals, in an integrated health care provider (Kaiser Permanente) database, exposed to BIS.[36] Incidence of AFF after 0.1 to 0.9 years of exposure was 1.78/100,000 persons/year, while incidence after 8 to 9.9 years of exposure was 113.1/100,000 persons/year.[36] The third study was a SR of studies on AFF and other outcomes,[37] where Dennison, 2019[19] reported an incidence of 3.0 to 9.8 AFFs per 100,000 person-years, and further described that the "relative risk increased with longer duration of [bisphosphonate] use, especially after more than 3 years […]"[19] (*p*.1738)

One additional primary study[35] in the Dennison, 2019[19] SR also had AFF results reported in the Fink, 2019[20] SR. The study was a combined cohort and case-control study of 172 cases of AFF and investigated their use of BISs.[35] Dennison, 2019[19] reported an absolute risk (AR) of 11 (95% CI, 7 to 14) AFFs per 10,000 person-years of BIS use.[19] After drug discontinuation, the risk decreased by 70% per year since the last use.[19] Fink, 2019[20] further stratified these data and expresses them as OR after three to four years of use (40; 95% CI, 17 to 91), four to five years (116; 95% CI, 58 to 234), and after five years of use (93; 95% CI, 66 to 132).[20]

One additional primary study[38] in the Fink, 2019[20] SR discussed AFFs. The primary study was a case-control comparing one or more year of current BIS use vs. past use.[38] The risk of AFFs with radiologic features was higher in current BIS users (HR = 3.36 [95% CI, 1.77 to 11.91] to 5.17 [95% CI, 2.0 to 13.36]).[20]

AE – Other Fracture Risk

Information regarding the effect of duration and course of BIS treatment for osteoporosis on the risks relative to other types of fractures was available from nine unique primary studies[29,30,32,33,40-44] included, with overlap, in four SRs.[19-22]

Two unique primary studies[41,42] in the Dennison, 2019[19] SR discussed risks relative to other types of fractures. The first was a cohort study of 160,369 women who had been established on BISs for three years with high refill compliance.[41] The risk of hip fracture at a median follow-up of 2.7 years was significantly increased in the treatment interruption group compared with the continued user group (adjusted HR = 1.22; 95% CI, 1.11 to 1.34; *P*-value not reported), and was 1.8-fold increased after four years.[19] The second study was a cohort study using the Swedish Prescribed Drug Register.[42] Participants who persisted with therapy for greater than one year had a 60% lower risk (RR = 0.40; P = 0.001) of fracture during the first six months after discontinuation when compared with those who discontinue therapy within the first year.[19]

One additional primary study[40] in the Dennison, 2019[19] SR also had results relative to other types of fractures reported in the Nayak, 2019[21] and the Eriksen, 2014[22] SRs. The study compared ALN 5mg for two years, then 10 mg for three years, then 5 mg for five years versus ALN 5 mg for two years, then 10 mg for eight years versus ALN 5 mg for two years, then 10 mg for three years, then placebo for five years.[40] Dennison, 2019[19] reported a reduced nonvertebral fracture risk (values not reported), in those *without* a vertebral fracture at baseline, favouring the 10 year ALN continuation group versus the five year ALN continuation group.[19] Nayak, 2019[21] and Eriksen, 2014[22] performed a different comparison,

reporting nonvertebral fracture risks, in those *without* a vertebral fracture at baseline, favouring the 10 year ALN continuation group (both dose groups combined) compared with the placebo group (RR = 0.50; 95% CI, 0.26 to 0.96).[21,22] Nayak, 2019[21] went on to report the morphometric vertebral fracture risks, in those *without* a vertebral fracture at baseline, as well as those *with* a vertebral fracture at baseline, also indicating in both cases that the results favoured the 10 year ALN continuation group (both dose groups combined) compared with the placebo group.[21] However, in those *with* a vertebral fracture at baseline, the nonvertebral fracture risk, favoured the placebo group compared with the 10 year ALN continuation group (both dose groups combined) (RR = 1.11; 95% CI, 0.61 to 2.02).[21] What is more, authors reported a clinical vertebral fracture risk favouring the 10 year ALN continuation group (both dose groups combined) compared with the placebo group (RR = 0.57; 95% CI, 0.23 to 1.40).[21]

Two primary study[29,30] in the Fink, 2019[20] SR also had results relative to other types of fractures reported in Nayak, 2019[21] SR. The first primary study compared ALN 5 mg for seven years versus ALN 10 mg for seven years versus ALN 20 mg for two years, followed by 5 mg for three years, followed by two years of placebo.[29] Nayak, 2019[21] reported the incidence of nonvertebral fracture between years six and seven as 6.6% (n = 8), 7.1% (n = 8), and 7.8% (n = 9) for the ALN 10 mg, 5mg, and placebo groups respectively,[21] while Fink, 2019[20] reported no between-group difference (both dose groups combined vs. placebo group) with a RR = 0.87 (95% CI, 0.40 to 1.91).[20] Nayak, 2019 reported that incidence of clinical vertebral fractures between years six and seven favoured the ALN 5 mg group,[21] while Fink, 2019[20] reported no between-group difference (both dose groups combined vs. placebo group) with a RR = 0.92 (95% CI, 0.40 to 2.10).[20] The second primary study compared ALN 5 mg for 10 years versus ALN 10 mg for 10 years versus ALN 20 mg for two years, followed by ALN 5 mg for three years, followed by five years of placebo.[30] Authors of Nayak, 2019[21] reported rates of first nonvertebral fracture between years eight and 10 favouring the ALN 10 mg group,[21] while Fink, 2019[20] reported no between-group differences (both dose groups combined vs. placebo group) with a RR = 0.81 (95% CI, 0.38 to 1.71).[20] As for morphometric vertebral fractures, Nayak, 2019[21] reported a non significant between-group difference (no effect estimate or *P*-value reported) between years six and 10.[21] Lastly, Fink, 2019[20] reported no between-group differences (both dose groups combined vs. placebo group) with a RR = 1.40 (95% CI, 0.52 to 3.74) for radiographic vertebral fractures.[20]

One additional primary study[43] in Fink, 2019[20] discussed risks relative to other types of fractures. The primary study was a case-control of 1,855 women aged 68 years or older and compared one or more year of current BIS use vs. past use.[43] There was a higher risk of subtrochanteric or femoral shaft fracture in those with greater than five years of use (OR = 2.74; 95% CI, 1.25 to 6.02) compared past users.[20]

Two unique primary studies[32,33] in the Nayak, 2019[21] SR discussed risks relative to other types of fractures. The first primary study compared a BIS holiday versus persistent (i.e., therapy adherence of 50% or more) users.[32] Adjusted hazard ratios (HR) for hip fractures, clinical vertebral fractures, and any osteoporotic fracture were no different between the BIS holiday group and the persistent use group.[21] The second primary study compared three years of BIS continuation versus a three year holiday in participants who had three to five years of BIS treatment.[33] The HR for clinical fractures (1.40; 95% CI, 1.12 to 1.60; P = 0.0095) favoured the continuation group (11.9%; n = 16/135) compared with the drug holiday group (16.1%; n = 5/31).[21] Nayak, 2019[21] also conducted a MA of fracture risks as reported in the two aforementioned studies[32,33] and reported a non significant adjusted HR

of any clinical osteoporotic fracture to be 1.13 (95% CI, 0.75 to 1.70) between individuals who discontinued BISs compared with those who continued therapy.[21] However, these results were in the presence of high statistical heterogeneity (I^2 = 94.3%).[21]

One unique primary study[44] in the Eriksen, 2014[22] SR reported a link between new morphometric vertebral fractures experienced by participants in the three years that followed a three year course of ZLN treatment and the participant's baseline BMD t-score and occurrence of morphometric vertebral fracture during the three year course of ZLN treatment.[22]

Other AEs

Information regarding the effect of treatment duration and courses of BISs for osteoporosis on other AEs was available from two unique primary studies[29,30] included, with overlap, in two SRs.[20,22]

Two primary study[29,30] in the Fink, 2019[20] SR also had results relative to other types of AEs reported in Eriksen, 2014[22] SR. The first primary study compared ALN 5 mg for seven years versus ALN 10 mg for seven years versus ALN 20 mg for two years, followed by 5 mg for three years, followed by two years of placebo.[29] Fink, 2019[20] reported no difference in risk for serious AEs (not defined), between the continuation groups (doses combined) and the placebo group, RR = 1.05 (95% CI, 0.57 to 1.96). Eriksen, 2014[22] went on to specify that there were no significant difference (*P*-value not reported) between groups in the incidence of AEs, upper gastrointestinal AEs, and placebo due to AEs.[22] The second primary study compared ALN 5 mg for 10 years versus ALN 10 mg for 10 years versus ALN 20 mg for two years followed by ALN 5 mg for three years followed by five years of placebo.[30] Fink, 2019[20] reported no difference in risk for serious AEs (not defined), between continuation (doses combined) and the placebo group, RR = 1.21 (95% CI, 0.75 to 1.96). Here too, authors of Eriksen, 2014[22] went on to specify that there were no significant difference (*P*-value not reported) between groups in the incidence of AEs, upper gastrointestinal AEs, and discontinuation due to AEs.[22] However, they reported four deaths (none considered associated with ALN treatment) in the ALN continuation groups (doses combined) compared with none in the placebo group.[22]

Evidence-Based Guidelines Regarding Length of Treatment with Bisphosphonates for Osteoporosis

Six guidelines[6,23-27] were identified regarding recommendations on the length of treatment with BISs for osteoporosis.

Duration of treatment

The first from the ACP, weakly recommends (based on low-quality evidence) a five year duration of treatment;[23] however, this recommendation is not specific regarding the type of pharmacological treatment.

The EMAS guidelines recommend (strength of evidence and recommendations not reported) the need to individualise treatment, taking into consideration the long-term efficacy of BISs, their safety, and the fracture risk of the patient.[24] Authors highlight that discontinuation of BISs should be considered in patients who have been treated for more than five years with ALN or more than three years with RSN, or ZLN (strength of evidence and recommendations not reported).[24]

The NOGG guidelines differ in their recommendations on treatment duration, recommending (grade C) that a review should be performed at three years with ZLN and 5 years with oral BISs (e.g., ALN, IBN, RSN).[25] A decision on treatment continuation beyond three years with ZLN and 5 years with oral BISs, can generally be recommended (evidence level IIb, grade of recommendation B) in PM "individuals age ≥75 years, those with a history of hip or vertebral fracture, those who sustain a fracture while on treatment, and those taking oral glucocorticoids".[25] (*p*.2) Authors further highlight that "There is no evidence to guide decisions beyond 10 years of treatment and management options in such patients should be considered on an individual basis".[25] (*p*.2)

The RACGP guidelines recommend (grade D) that clinicians reconsider the need for BIS therapy after five to 10 years in PM women and men over 50 years of age with osteoporosis, when their BMD t-score is –2.5 or higher and there are no recent fractures.[26] If this BMD t-score threshold is not met or if there are new vertebral fractures, authors recommend (grade D) treatment continuation.[26]

The *SEIOMM* guidelines do not indicate a particular treatment duration and recommend (grade D) that "treatment should last as long as necessary to decrease the risk of fractures to acceptable levels".[27] (*p*.521) Authors suggest that a BMD t-score above –2.5 standard deviations and no recent fractures, or a BMD t-score above –2 standard deviations and one previous fracture could constitute an "acceptable level".[27] They recommend (grade D) reassessing patients every three to five years and discontinue treatment once this "acceptable level" is achieved.[27]

The WRHA guidelines recommend (grade D) that osteoporosis therapy should continue in individuals at high risk for fracture.[6] While they recommend (strength of evidence and recommendations not reported) that individuals at moderate risk should have their osteoporosis therapy reassess every three to five years for the need to continue, discontinue, or initiate a drug holiday.[6]

Duration of drug holiday

The EMAS guidelines highlight the need to re-evaluate patients one to three years after BIS discontinuation and that the decision to resume treatment ought to depend on a reassessment of risk factors, new fractures, and possibly BMD (strength of evidence and recommendations not reported).[24]

Similarly, the NOGG guidelines recommend (grade C) the need to re-evaluate patients where treatment has been discontinued, either after 18 months to three years, or after a new fracture.[25] Authors recommend (grade B) a reassessment of fracture risk using the FRAX tool or with femoral neck BMD. Also, if biochemical markers indicate a relapse from suppressed bone turnover and BMD has decreased following withdrawal, authors recommend (grade C) that resumption of treatment should be considered.[25]

The RACGP guidelines recommend (grade D) that treatment should be restarted if there is evidence of bone loss, especially at the hip, or if a further minimal trauma fracture is sustained.[26] The re-assessment of these parameters are recommended (grade B) to be performed on an regular basis (frequency not specified).[26]

Limitations

A number of limitations were identified in the critical appraisal as shown in Appendix 3, Table 4 and Table 5; however, additional limitations exist. The main limitations of this review are related to the heterogeneity of the study populations and the generalizability of the findings. Heterogeneity was apparent in the baseline patient characteristics, such as BMD, past fracture history, and past use of osteoporosis medication. Also, because SR data were often available only at the study level, it remains unclear whether any differences between outcomes were due to differences in population characteristics.

Eight of the 17 included primary studies were cohort or case-control studies,[32,33,35-37,39,42,43] with associated methodological limitations. Furthermore, some primary studies may have been too small to examine uncommon clinical events, as noted by the wide confidence intervals for some endpoints. In addition, there was an overall lack of comparative statistical analyses between treatment groups, and when performed, were usually done post-hoc.

Except for primary studies that queried databases for prescription refill statistics,[41,42] participant's adherence with treatment was not reported which introduces uncertainty with regards to the magnitude of effects reported in the SRs.

Two SRs[19,22] did not perform a quality assessment of their included studies, which limits the overall reliability of their results. While the other two SRs[20,21] reported that studies relevant to this report had a low or unclear risk of bias, introducing uncertainty in their results.

At least one SR[20] inferred fracture risk data from studies not designed to compared fracture incidence between groups. Their results on between-group relative risk differences of fractures may lead to incorrect conclusions.

All SRs[19-22] reported results without providing some, or all, associated *P*-values (where appropriate), which may have introduced an outcomes reporting bias, limiting the overall reliability of their results.

The applicability of the evidence to the Canadian setting is unclear since the country of origin of SR primary studies was inconsistently reported and only one evidence-based guideline was developed in Canada.

Guideline recommendations were generally based on low-quality evidence,[23,25-27] or did not consistently report the strength of evidence and recommendations.[6,24]

Although two SRs[20,21] included males in their population eligibility criteria, one included primary studies[35] reported on this population; therefore, generalizability of results in males is unclear. This also suggests that additional research in this population is required.

Although data were identified regarding when to initiate a drug holiday, there was no clear evidence that emerged from the literature on the optimal duration of a drug holiday, suggesting that additional research in this area is required.

Conclusions and Implications for Decision or Policy Making

This report identified clinical evidence and evidence-based guidelines regarding treatment durations and courses of BISs for osteoporosis. One HTA,[18] four SRs,[19-22] including one with MA,[20] and six guidelines[6,23-27] were identified and included in this review. The HTA,[18]

met the inclusion criteria for this report; however, none of the primary studies included in the HTA met the eligibility criteria for this report; therefore, no summary could be provided.

The identified literature were heterogenous and revealed mixed conclusions regarding clinical evidence of treatment duration and courses of BISs for osteoporosis. No clear direction emerged regarding BMD results, most of which were non-statistically significant and between group comparisons were difficult because of heterogeneity in BIS used, the location of BMD measurements, the time point of the measurement, the duration of use, and participant's history of fracture at baseline.[19,21,22] Antifracture efficacy results favoured the drug continuation group for six years (ZLN) or seven (ETN).[21] AFF results came mostly from cohort studies, which all concluded that an increased incidence occurred with increased duration of BIS use;[19,20] however, the risk decreased by 70% per year after discontinuation.[19] No clear direction emerged regarding risks related to other types of fractures, which favoured the drug discontinuation group or continuation group depending on the BIS used, the dose, the duration of use, the participant's history of fracture at baseline, and the type of fracture sustained.[19-22] Other types of AEs were generally reported as no different between the drug continuation groups and discontinuation groups,[20,22] except for four deaths (none considered associated with treatment) in a continuation group compared with none in the placebo group.[22]

Evidence-based guidelines offer no clear direction on duration of BIS treatment. Two guidelines recommend a three to five year duration of treatment,[23,24] one recommends five to 10 years,[26] while others suggest an indeterminate period.[6,25,27] However, most guidelines nuance their recommendations by advocating for regular patient monitoring and the individualisation of treatment in response to clinical and paraclinical manifestations.[6,10,23-27] Similarly, they offer no clear direction on duration of BIS drug holidays, but rather to base the decision on a periodic reassessment of the patient.[24-26]

The limitations of the included studies should be considered when interpreting the results. The findings highlighted in this review come with a high degree of uncertainty. Further research investigating the clinical evidence of treatment duration and courses of BISs for osteoporosis, especially by way of large, methodologically-sound RCTs or well-designed meta-analyses, would help reduce this uncertainty.

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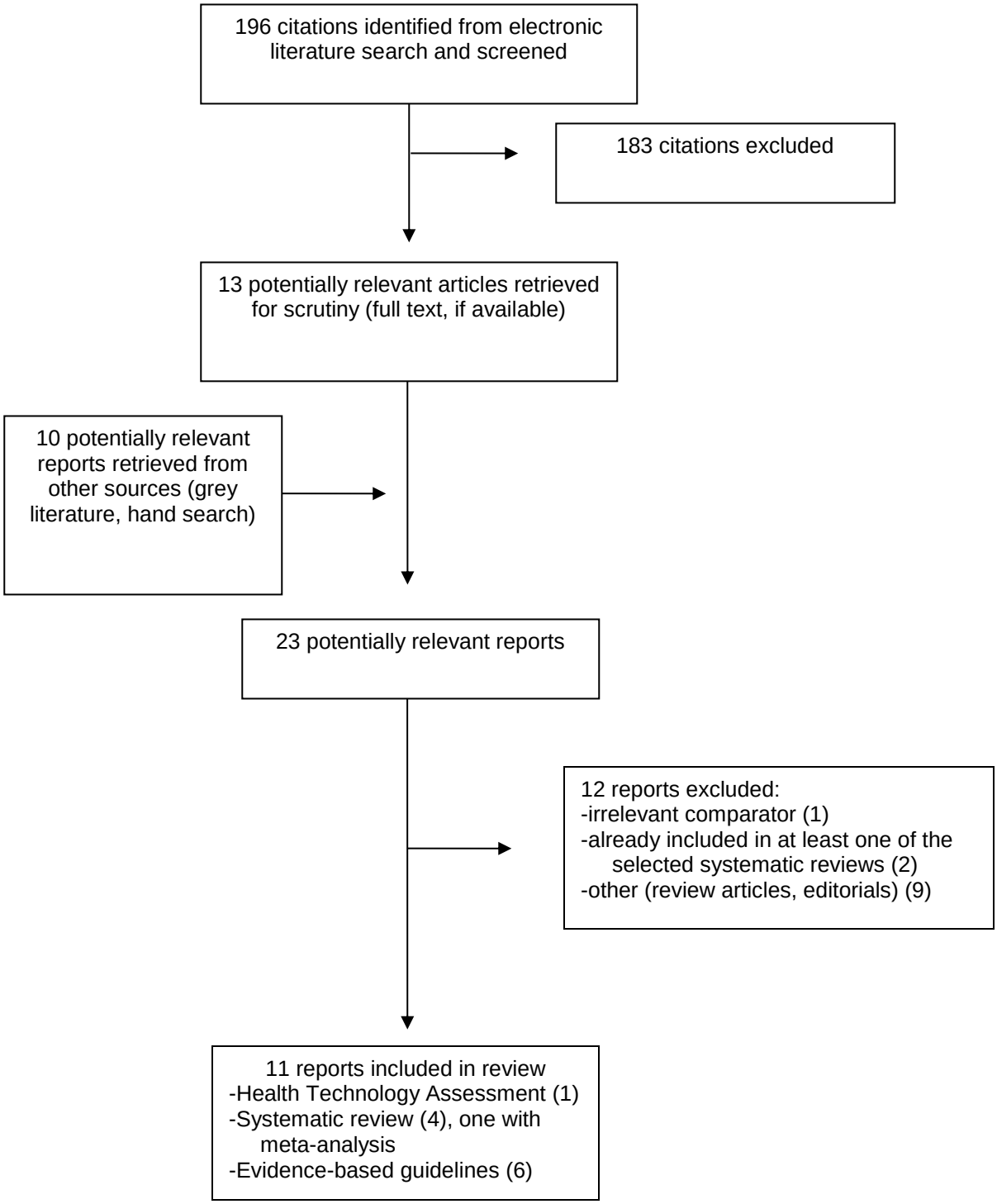
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Health Technology Assessment, Systematic Reviews, and Meta-Analysis

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Health Technology Assessment				
Davis, 2016[18] United Kingdom	**Study design**: SR including NMA of relevant RCTs and NRSs **Literature search strategy**: Authors performed literature searches in several databases including: MEDLINE, EMBASE, the Cochrane Library, CINAHL, Web of Science, BIOSIS preview, Clinicaltrials.gov, and WHO International Clinical Trials Registry Platform from 2008 until September 2014. No limiters were applied to study retrieval. **Number of studies included**: In total, 59 articles were included; however, none were relevant to this report. **Quality assessment tool**: The Cochrane Risk of Bias Tool. **Objective**: To evaluate the clinical effectiveness, safety, and cost-effectiveness of BISs for the prevention of fragility fractures.	Women 65 years of age or older or men 75 years of age or older. Alternatively, study participants could be younger if they also presented with certain risk factors.	**Interventions**: • BISs **Comparators**: • BISs compared to each other • placebo • Other non-active treatment	**Relevant Outcomes:** • Fragility fractures • BMD at the femoral neck • Mortality • AEs • Compliance • HRQoL • Health care resource use **Follow-up:** not applicable
Systematic Reviews and Meta-Analysis				
Dennison, 2019[19] United Kingdom	**Study design**: SR of relevant RCTs and observational studies. **Literature search strategy**: Authors performed literature searches in PubMed, EMBASE, Cochrane library, NHS Evidence, Epistemonikos, and NIH trial registry records	PM women on osteoporosis medication for 1 y or more. **Included studies**: • A secondary analysis[40] of the FLEX RCT study: PM women 61	**Interventions**: BISs (i.e., ALN, RSN, IBN, ZLN) or denosumab **Comparators**: Medication continuation versus discontinuation	**Relevant Outcomes:** • Bone turnover markers (types not specified) • BMD

Table 2: Characteristics of Included Health Technology Assessment, Systematic Reviews, and Meta-Analysis

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	for the period of 2011 to 2016. This was supplemented by a search of relevant conference abstracts for 2017 to 2018. **Number of studies included**: In total, 38 articles were included, with nine relevant for this review: a secondary analysis[40] of the FLEX RCT study, a SR,[37] cohort studies,[33,35,36,39,41,42] and case-control studies.[35,39] Note that Mignot, 2017[33] and Schwartz, 2010[40] are also included in the Nayak, 2019[21] SR herein. Similarly, Schilcher, 2015[35] is also included in the Fink, 2019[20] SR herein, and Schwartz, 2010[40] is also included in the Eriksen, 2014[22] SR herein. **Quality assessment tool**: NR **Objective**: To review the clinical evidence on osteoporosis therapy duration and decision making around continuation or discontinuation of therapy.	to 86 y old, previously treated with 4 or 5 y of ALN. • SR: 23 studies on AFF,14 on epidemiology, and 11 on treatment outcomes.[37] • Cohort study: 160,369 women who had been established on BISs for 3 y with high refill compliance.[41] • Cohort study: using the Swedish Prescribed Drug Register.[42] • Cohort study: 188,814 individuals in Kaiser Permanente database exposed to BIS: 142 cases of AFF[36] • A combined cohort and case-control study: 59 cases of AFF and 263 controls, while on BIS therapy.[39] • A combined cohort and case-control study: 172 cases.[35] • Cohort study: 183 PM women with osteoporosis who continued or discontinued BISs for 3 to 5 y.[33]		• Fracture • Osteonecrosis of the jaw • AFF **Follow-up:** NR
Fink, 2019[20] United States of America	**Study design**: SR with MA of relevant trials and observational studies. **Literature search strategy**: Authors performed literature searches in MEDLINE, EMBASE, and the Cochrane library for the period of Jan 1995 to Oct 2018. This was supplemented by a hand search of bibliographies and a search of trial registry records. Results were limited to English language studies.	Men or PM women aged 50 y or older who were being investigated or treated for fracture prevention. **Included studies**: • Two extensions of a phase III RCT, the first in 350 PM women with osteoporosis,[29] and the second in 247 PM women with osteoporosis.[30] • A combined cohort and case-control study: 172 cases.[35]	**Interventions**: Long-term (i.e., 3 or more y) osteoporosis drug treatments **Comparators**: • Control, • Continuation versus discontinuation (cessation for 1 or more y after 1 or more y of use) **Included studies**:	**Relevant Outcomes:** • Incidence of clinical fractures • Incidence of radiographic fractures • DXA BMD • AEs **Follow-up:** 3 or more years of

Table 2: Characteristics of Included Health Technology Assessment, Systematic Reviews, and Meta-Analysis

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Number of studies included: In total, 48 articles were included, with 5 relevant for this review: 2 extensions[29,30] of a phase III RCT, a combination cohort case-control study,[35] and two case-control studies.[38,43] Note that Bone, 2004[30] and Tonino, 2000[29] are also included in the Nayak, 2019[21] SR herein. Similarly, Schilcher, 2015[35] is included in the Dennison, 2019[19] SR herein. **Quality assessment tool**: Risk of bias and strength of the evidence were assessed using criteria from the AHRQ. **Objective**: To review the effects of long-term osteoporosis drug treatment, discontinuation, and holidays.	• Case-control: 172 PM women.[38] • Case-control: 1,855 women aged 68 y or older.[43]	• Two extensions of a phase III RCT comparing ALN 5 mg or 10 mg for 7 y[29] or 10 y[30] vs. ALN 20 mg for 2 y, then 5 mg for 3 y, then placebo for 2 y[29] or 5 y.[30] • Cohort and case-control comparing BIS vs. no BIS.[35] • Case-control comparing one or more year of current BIS use vs. past use.[38] • Case-control comparing one or more year of current BIS use vs. past use.[43]	treatment, 1 or more year of discontinuation after one or more year of use.
Nayak, 2019[21] United States of America	**Study design**: SR of relevant clinical studies, controlled trials, and cohort studies. **Literature search strategy**: Authors performed literature searches in PubMed, EMBASE, and the Cochrane Library up to January 2018. This was supplemented by a manual search of the reference lists of included studies. No limiters were applied to study retrieval. **Number of studies included**: In total, 13 articles were included, with 7 relevant for this review: An extension[8] of the HORIZON-PFT study, a secondary analysis[40] of the FLEX RCT study, 2 extensions[29,30] of a phase III RCT, an extension study[34] of an RCT, and cohort studies.[32,33]	Participants with osteoporosis or osteopenia who had received osteoporosis treatment for at least 3 y. **Included studies**: • RCT: 1,233 PM women who previously received ZLN for 3 y for osteoporosis.[8] • Secondary analysis[40] of the FLEX RCT study: 1,099 PM women 61 to 86 y old, previously treated with 4 or 5 y of ALN. • Two extensions of a phase III RCT, the first in 350 PM women with osteoporosis,[29] and the second in 247 PM women with osteoporosis.[30]	**Interventions**: • Continue treatment **Comparators**: • Discontinue treatment (drug holiday) **Included studies**: • RCT comparing ZLN for 6 y vs. ZLN for 3 y plus 3 y of placebo,[8] • A secondary analysis[40] of the FLEX RCT study, which compared continuing ALN (various doses) after 5 y vs. discontinuing (placebo).	**Relevant Outcomes:** • BMD • Fracture risk **Follow-up:** Not applicable

Table 2: Characteristics of Included Health Technology Assessment, Systematic Reviews, and Meta-Analysis

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Note that Schwartz, 2010,[40] Bone, 2004,[30] and Tonino, 2000[29] are also included in the Eriksen, 2014[22] SR herein. Similarly, Bone, 2004,[30] and Tonino, 2000[29] are also included in the Fink, 2019[20] SR herein, as well as Mignot, 2017[33] and Schwartz, 2010[40] are also included in the Dennison, 2019[19] SR. **Quality assessment tool**: for clinical trials: the Cochrane Collaboration's risk of bias tool. For cohort studies: the Newcastle-Ottawa quality assessment scale. **Objective**: To summarize the evidence on the effect of osteoporosis treatment drug holidays or discontinuation on BMD and fracture risk.	• An extension study of an RCT of 193 PM women[34] • Cohort: 39,502 women aged 45 y or older with 3 or more y of prior BIS use with 50% or greater adherence.[32] • Cohort: 183 PM women with osteoporosis who continued or discontinued BISs for 3 to 5 y.[33]	• Two extensions of a phase III RCT comparing ALN 5 mg or 10 mg for 7 y[29] or 10 y[30] vs. ALN 20 mg for 2 y, then 5 mg for 3 y, then placebo for 2 y[29] or 5 y.[30] • An extension study of an RCT of ETN or placebo for 3 y, then all participants received ETN for years 4 and 5, then a re-randomization to ETN or placebo for years 6 and 7.[34] • Cohort comparing BIS holiday (average of 3.1 y long after an average of 5.2 y of prior use) vs. persistent users (i.e., 50% or greater adherence) and non-persistent users (i.e., less than 50% adherence).[32] • Cohort comparing continuation or discontinuation of BISs (44% ALN, 40% RSN, 11% ZLN, 5% IBN).[33]	
Eriksen, 2014[22] Norway	**Study design**: SR of relevant controlled clinical trials. **Literature search strategy**: Authors performed a literature search in PubMed up to January 2013. **Number of studies included**: In total, 9 articles were included, with 4 relevant for this review: two extensions[13,14] of a phase III RCT,[29,30] a secondary analysis[40] of the FLEX RCT study, and a secondary analysis[44] of the HORIZON-PFT study.	Participants were PM women with osteoporosis **Included studies**: • Two extensions of a phase III RCT, the first in 350 PM women with osteoporosis,[29] and the second in 247 PM women with osteoporosis.[30] • A secondary analysis[40] of the FLEX RCT study: 1,099 PM women 61 to 86 y old, previously treated with 4 or 5 y of ALN.	**Interventions**: Continued treatment with either: • ALN • RSN • IBN • ZLN **Comparators**: • Discontinuation of treatment **Included studies**: • Two extensions of a phase III RCT comparing ALN 5 mg or	**Relevant Outcomes:** • BMD • Fracture • AEs **Follow-up:** Not applicable

Table 2: Characteristics of Included Health Technology Assessment, Systematic Reviews, and Meta-Analysis

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Note that Schwartz, 2010,[40] Bone, 2004,[30] and Tonino, 2000[29] are also included in the Nayak, 2019[21] SR herein. Similarly, Bone, 2004,[30] and Tonino, 2000[29] are also included in the Fink, 2019[20] SR herein, and Schwartz, 2010[40] is also included in the Dennison, 2019[19] SR. **Quality assessment tool**: NR **Objective**: To summarize the long-term data relating to BISs in PM women with osteoporosis.	• A secondary analysis of the HORIZON-PFT study: 1,223 women who had already received 3 y of ZLN.[44]	10 mg for 7 y[29] or 10 y[30] vs. ALN 20 mg for 2 y, then 5 mg for 3 y, then placebo for 2 y[29] or 5 y.[30] • A secondary analysis[40] of the FLEX RCT study, which compared continuing ALN (various doses) after 5 y vs. discontinuing (placebo). • A secondary analysis of the HORIZON-PFT study which compared 6 y of ZLN vs. 3 y of ZLN plus 3 y of placebo.[44]	

AE = adverse event; AFF = atypical femoral fractures; AHRQ = Agency for Healthcare Research and Quality; ALN = alendronate; BIOSIS = BioSciences Information Service of Biological Abstracts; BIS = bisphosphonate; BMD = bone mineral density; CINAHL = Cumulative Index to Nursing and Allied Health Literature; DXA = dual-energy x-ray absorptiometry; EMBASE = Excerpta Medica database; ETN = etidronate; FLEX = Fracture Interventional Trial Long Term Extension; HORIZON-PFT = Health Outcomes and Reduced Incidence with Zoledronate One Yearly – Pivotal Fracture Trial; HRQoL = health related quality of life; IBN = ibandronate; MEDLINE = Medical Literature Analysis and Retrieval System Online; NHS = National Health Service; NIH = National Institutes of Health; NMA = network meta-analysis; NR = not reported; PM = postmenopausal; PubMed = public MEDLINE; RCT = randomized controlled trial; RSN = risedronate; SR = systematic review; WHO = World Health Organisation; ZLN = zoledronic acid.

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
American College of Physicians, 2017, United States of America[23]						
Intended users: All clinicians **Target population**: Adults with low BMD or osteoporosis	BISs (ALN, RSN, IBN, ZLN), denosumab, teriparatide, selective estrogen receptor modulators, estrogen, calcium, vitamin D	Reduction in fractures (total, vertebral, nonvertebral, spine, hip, wrist, other); AEs	AHRQ conducted a SR of literature published between January 2, 2005 and June 3, 2011. The review was updated to October 2016 using PubMed.	GRADE system, AGREE II	CGC used an informal process to evaluate and formulate the recommendations based on evidence. The final recommendations are voted by CGC members and ACP's Board of Regent.	Guideline undergoes Independent peer-review at Annals of Internal Medicine. Occasionally, external reviewers and experts are invited.
European Menopause and Andropause Society, 2017, Greece[24]						
Intended users: NR **Target population:** PM women or older men (50 y or older) diagnosed with osteoporosis	BISs (ALN, RSN, ZLN), denosumab	Fracture risk, AEs	SR of literature published up to January 31, 2017 with searches in MEDLINE, Scopus, EMBASE, and Cochrane databases.	NR	Three independent researchers reviewed eligible studies during systematic review. Recommendations were reviewed by EMAS board members.	Not externally peer reviewed
National Osteoporosis Guideline Group, 2017, United Kingdom[25]						
Intended users: Health care professionals involved in osteoporosis management	BISs (ALN, RSN, IBN, ZLN), denosumab, teriparatide, selective estrogen receptor modulators,	Not specified, fracture risk, AEs	Where available, SRs, MAs, and RCTs were used to form the evidence base. PubMed searches were conducted.	SRs and MAs were graded using AMSTAR. Recommendations were systematically graded based on the level of evidence.	The National Osteoporosis Guideline Development Writing Group, consisting of the Guideline Development Group and Expert Advisory Group, provided the guideline	Recommendations were reviewed by stakeholders and external reviewers

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Target population: PM women or older men (50 y or more)	estrogen, calcium, vitamin D			• **Grade A** = evidence levels Ia (from MAs of RCTs) and Ib (from at least one RCT) • **Grade B** = evidence levels IIa (from at least one NRS), IIb (from at least one other type of quasi-experimental study) and III (from non-experimental studies) • **Grade C** = evidence level IV (from expert opinion)	content. Only the Guideline Development Group was involved in the voting of recommendations. .	
Royal Australian College of General Practitioners, 2017, Australia[26]						
Intended users: Health care professionals involved in osteoporosis management in older patients **Target population:** PM women or older men (50 y or older) diagnosed with osteoporosis	BISs (ALN, RSN, IBN, ZLN), denosumab, teriparatide, selective estrogen receptor modulators, estrogen, Strontium ranelate, calcium, vitamin D	Fracture, BMD	SR of literature published between 2006 and February 2016. Some studies used for the 2010 guideline are included.	NHMRC grades of recommendation: • **Grade A** = Body of evidence can be trusted to guide practice • **Grade B** = Body of evidence can be trusted to guide practice in most situations • **Grade C** = Body of evidence provides some support for recommendation, but care should	Twelve-member expert Working Group developed recommendations through review of literature, and Working Group consensus when insufficient evidence was available	Review by GP subject matter experts and the RACGP's Expert Committee for Quality Care. The guideline was also endorsed by the RACGP Council.

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
				be taken in its application • **Grade D** = Body of evidence is weak, and recommendation must be applied with caution		
Spanish Society for Research on Bone and Mineral Metabolism, 2015, Spain[27]						
Intended users: Unable to assess (full guideline not available in English) **Target population:** PM women or men diagnosed with osteoporosis	BISs (ALN, ETN, RSN, IBN, ZLN), denosumab, teriparatide, selective estrogen receptor modulators, Strontium ranelate, calcium, vitamin D	Not specified, fracture risk, AEs	Unable to assess. Multiple databases used (MEDLINE, Cochrane, CINAHL).	OCEBM criteria used for levels of evidence. OCEBM grades of recommendation: • **Grade A** = consistent level 1 studies (RCTs) • **Grade B** = consistent level 2 (cohort) or level 3 (case-control) studies or extrapolations of level 1 studies • **Grade C** = level 4 studies (case series & low-quality cohort or case-control studies) or extrapolations of level 2/3 studies • **Grade D** = level 5 tests (expert opinions, inconclusive	Unable to assess	Unable to assess

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
				studies or inconsistency problems)		
Winnipeg Regional Health Authority, 2014, Canada[6,10]						
Intended users: Health care providers in Manitoba, including direct care staff, policy makers, educators, administrators and interprofessional care team members **Target population:** Women and men over age 50	BISs (ALN, RSN, ZLN), denosumab, teriparatide, selective estrogen receptor modulators, calcium, vitamin D	Not specified, fracture risk	SR of literature on fracture risk assessment published between Jan 1990 to September 19, 2010. To identify further studies, they used an existing SR on osteoporosis therapies by MacLean *et al.,* 2008[45]	Recommendations were graded based on the level of evidence. • **Grade A** = Need supportive level 1+ (systematic overview of MA of RCTs) or 1 (adequately powered RCTs) evidence plus consensus • **Grade B** = Need supportive level 2+ (systematic overview or MA of level 2 RCTs) or 2 (RCTs that do not meet level 1 criteria) evidence plus consensus • **Grade C** = Need supportive level 3 (NRS or cohort studies) evidence plus consensus • **Grade D** = Any lower level of evidence (before-after, case-control, case series, case	The Best Practice Guidelines Committee, consisting of participants from across Canada with methodological and content expertise, drafted the guidelines. An expert panel, consisting of members of the Osteoporosis Canada Scientific Advisory Council, members of stakeholder organizations, family physicians and experts from across Canada, used a modified Delphi method to discuss the recommendations.	The Guidelines Committee and the Executive Committee of the Osteoporosis Canada Scientific Advisory Council reviewed the recommendations.

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
				report studies) supported by consensus		

ACP = American College of Physicians; AE = adverse event; AGREE II = Appraisal of Guidelines for Research and Evaluation Instrument II; AHRQ = Agency for Healthcare Research and Quality; ALN = alendronate; AMSTAR = A MeaSurement Tool to Assess systematic Reviews; BIS = bisphosphonate; BMD = bone mineral density; CGC = clinical guidelines committee; CINAHL = Cumulative Index to Nursing and Allied Health Literature; EMAS = European Menopause and Andropause Society; ETN = Etidronate; GP = general practitioner; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; IBN = ibandronate; MA = meta-analysis; MEDLINE = Medical Literature Analysis and Retrieval System Online; NHMRC = National Health and Medical Research Council; NOGG = National Osteoporosis Guideline Group; NR = not reported; NRS = non-randomized study; OCEBM = Oxford Centre for Evidence-Based Medicine; PM = postmenopausal; PubMed = public MEDLINE; RACGP = Royal Australian College of General Practitioners; RCT = randomized controlled trial; RSN = risedronate; SEIOMM = Spanish Society for Research on Bone and Mineral Metabolism; SR = systematic review; WRHA = Winnipeg Regional Health Authority; ZLN = zoledronic acid.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Included Health Technology Assessment, Systematic Reviews, and Meta-Analysis using AMSTAR 2[16]

Strengths	Limitations
Health Technology Assessment	
Davis, 2016, United Kingdom[18]	
• The review has a clear population, intervention, comparator, and outcomes as inclusion criteria • An a priori protocol was registered with PROSPERO (CRD42013006883) • The choice of included study designs was justified • Review authors used a comprehensive literature search strategy, included additional references identified via the bibliography of eligible studies, contacted experts in the field, and sought out grey literature • Study selection and data extraction were performed in duplicate • A list of excluded studies was provided • Authors assessed the risk of bias in the RCTs using the Cochrane risk of bias tool. Attrition of 10% or greater was found in 63% of included studies, 5 trials were either open label or single blind and therefore at high risk of performance bias, and 28% of studies reported assessing outcomes in a blinded manner.[18] • Risk of bias in individual studies was accounted for in the interpretation and discussion of the results of the review • Authors reported their competing interests and they are unlikely to have influenced the results of the review • Review authors reported on source of funding for the included studies • Source of funding for the review was disclosed (National Institute for Health Research) and editorial independence was reported	• Although the search strategy was thorough, a formal assessment of publication bias was not undertaken
Systematic Reviews and Meta-Analysis	
Dennison, 2019, United Kingdom[19]	
• Inclusion criteria for the review has a clear population, intervention, comparator, and outcomes • Source of funding for the review were disclosed and editorial independence was reported	• Reporting discrepancies were identified between the SR and some primary studies • Referencing discrepancies were also identified, where the bibliographic references didn't match the citation • An a priori protocol was not reported for the review • The choice of included study designs was not justified

Table 4: Strengths and Limitations of Included Health Technology Assessment, Systematic Reviews, and Meta-Analysis using AMSTAR 2[16]

Strengths	Limitations
	• Although the search strategy was provided, publication restrictions are not justified. Also, it was not clear if the reference lists of included studies were searched, and if trial/study registries were searched • The quality of included studies was not assessed • Study selection and data extraction were not reported as completed in duplicate • A list of excluded studies was not provided • Included studies were not described in detail • A satisfactory technique for assessing the risk of bias in included studies was not reported • Risk of bias in individual studies was not accounted for in the interpretation and discussion of the results of the review • Review authors did not report on source of funding for the included studies • Although authors reported their competing interested, a statement on how these were managed was not included
Fink, 2019, United States of America[20]	
• Inclusion criteria for the review has a clear population, intervention, comparator, and outcomes • An a priori protocol was registered with PROSPERO (CRD42018087006) • The choice of included study designs was justified • Review authors used a comprehensive literature search strategy and they included additional references identified via the bibliography of eligible studies, as well as grey literature if it included sufficient information to assess eligibility and risk of bias • Study selection and data extraction were performed in duplicate • Authors assessed the risk of bias for outcomes of interest as low, medium, or high on the basis of criteria from the AHRQ • Risk of bias in individual studies was accounted for in the interpretation and discussion of the results of the review • Authors reported their competing interests and they are unlikely to have influenced the results of the review • Source of funding for the review were disclosed and editorial independence was reported	• A list of excluded studies was not provided • Review authors did not report on source of funding for the included studies
Nayak, 2019, United States of America[21]	

Table 4: Strengths and Limitations of Included Health Technology Assessment, Systematic Reviews, and Meta-Analysis using AMSTAR 2[16]

Strengths	Limitations
• Inclusion criteria for the review has a clear population, intervention, comparator, and outcomes • Review authors used a comprehensive literature search strategy which included a hand search of the bibliography of eligible studies. However, it is not clear if they searched trial registries or attempted to retrieve grey literature • Authors assessed the risk of bias in individual studies using the Cochrane Collaborations' risk of bias tool for clinical trials and the Newcastle-Ottawa quality assessment scale for cohort studies • Review authors extracted information on source of funding for the included studies, but it was not reported • The authors justified combining the data in a meta-analysis and they used a random-effects (DerSimonian and Laird) method, to calculate summary effect size estimates • Risk of bias in individual studies was accounted for in the interpretation and discussion of the results of the review • Authors reported their competing interests (none) • Source of funding for the review were disclosed and it was unlikely to have influenced the findings of the review	• An a priori protocol was not reported for the review • The choice of included study designs was not justified • Study selection and data extraction were not reported as being performed in duplicate • A list of excluded studies was not provided • Although between-study heterogeneity was assessed, they did not discuss the likely impact on the results • Potential publication bias was not reported, therefore its likely impact on the results of the review could not be assessed.
Eriksen, 2014, Norway[22]	
• The choice of included study designs was justified • Source of funding for the review were disclosed (no funding received) and editorial independence declared	• Although authors described the population and intervention inclusion criteria for the review, it was not clear what comparator and outcomes were of interest, if any • An a priori protocol was not reported for the review • Review authors did not use a comprehensive literature search strategy. Only one database was searched and there was no mention of hand searching the bibliography of eligible studies, searching trial registries, or attempting to retrieve grey literature • Study selection and data extraction were not reported as being performed in duplicate • A list of excluded studies was not provided • Included studies were not described in adequate detail and there was poor consistency in reporting the population, intervention, comparator, and research design • Quality of included studies as well as risk of bias were not assessed • Authors did not report on the source of funding of the included studies

Table 4: Strengths and Limitations of Included Health Technology Assessment, Systematic Reviews, and Meta-Analysis using AMSTAR 2[16]

Strengths	Limitations
	• Although authors noted that there was heterogeneity of the populations, interventions, and lengths of follow up, they did not discuss its likely impact on the results • Although authors reported their competing interests (such as those with drug manufacturers), they did not discuss the manner by which these were managed, therefore we could not assess how these may have influenced the review findings

AHRQ = Agency for Healthcare Research and Quality; PROSPERO = International prospective register of systematic reviews; SR = systematic review.

Table 5: Strengths and Limitations of Guidelines using AGREE II[46]

Item	Guideline					
	American College of Physicians, 2017[23]	European Menopause and Andropause Society, 2017[24]	National Osteoporosis Guideline Group, 2017[25]	Royal Australian College of General Practitioners, 2017[26]	Spanish Society for Research on Bone and Mineral Metabolism, 2015[27]	Winnipeg Regional Health Authority, 2014[6,10]
Domain 1: Scope and Purpose						
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes	Yes	Yes
Domain 2: Stakeholder Involvement						
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Yes	Yes	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No	No	No	No	Unable to assess[a]	No
6. The target users of the guideline are clearly defined.	Yes	No	Yes	Yes	Unable to assess[a]	Yes
Domain 3: Rigour of Development						
7. Systematic methods were used to search for evidence.	Yes	Yes	Yes	Yes	Unable to assess[a]	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes	Yes	Yes	Yes	Yes

Table 5: Strengths and Limitations of Guidelines using AGREE II[46]

Item	Guideline					
	American College of Physicians, 2017[23]	European Menopause and Andropause Society, 2017[24]	National Osteoporosis Guideline Group, 2017[25]	Royal Australian College of General Practitioners, 2017[26]	Spanish Society for Research on Bone and Mineral Metabolism, 2015[27]	Winnipeg Regional Health Authority, 2014[6,10]
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes	Yes	Yes	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	No	Yes	Yes	Unable to assess[a]	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes	Yes	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	No	Yes	Yes	Unable to assess[a]	Yes
14. A procedure for updating the guideline is provided.	Yes	No	Yes	Yes	Unable to assess[a]	No
Domain 4: Clarity of Presentation						
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes	Yes	Yes
Domain 5: Applicability						

Table 5: Strengths and Limitations of Guidelines using AGREE II[46]

Item	Guideline					
	American College of Physicians, 2017[23]	European Menopause and Andropause Society, 2017[24]	National Osteoporosis Guideline Group, 2017[25]	Royal Australian College of General Practitioners, 2017[26]	Spanish Society for Research on Bone and Mineral Metabolism, 2015[27]	Winnipeg Regional Health Authority, 2014[6,10]
18. The guideline describes facilitators and barriers to its application.	Not within scope	Not within scope	Yes	Yes	Unable to assess[a]	Not within scope
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes	Yes	Yes	Unable to assess[a]	Yes
20. The potential resource implications of applying the recommendations have been considered.	Not within scope	Not within scope	Yes	Yes	Unable to assess[a]	Not within scope
21. The guideline presents monitoring and/or auditing criteria.	Yes	Yes	Yes	Yes	Yes	Yes
Domain 6: Editorial Independence						
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes	Yes	Yes	Unable to assess[a]	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes	Yes	Unable to assess[a]	Yes

NOTE:

[a] The integral version of this guideline is only available in Spanish, restricting the assessment of strengths and limitations to information that is published in the English summary[27]

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings in Included Health Technology Assessment, Systematic Reviews and Meta-Analysis

Main Study Findings	Authors' Conclusion
Systematic Reviews and Meta-Analysis	
Dennison, 2019[19]	

BMD
 	
Cohort,[33] (Note results from Mignot, 2017[33] are also included in the Nayak, 2019[21] SR herein)
• "BMD trends were similar in patients who sustained a fracture during the holiday versus those who did not sustain."[19] (*p*.1737) (effect estimates were not provided)
 	
Adverse events
 	
SR;[37]
• Incidence of **AFF** = 3.0 to 9.8 per 100,000 person-years; however, the "relative risk increased with longer duration of [bisphosphonate] use, especially after more than 3 y […]"[19] (*p*.1738)
 	
RCT, secondary analysis[40] of FLEX study (Note that results from Schwartz, 2010[40] are also included in the Nayak, 2019[21] SR herein):
• **Non-vertebral fractures** in women without prevalent vertebral fracture whose femoral neck T-score are –2.5 or less at 5 y:
  ○ ALN for 10 y = reduced risk (values not reported)
  ○ ALN for 5 y, then placebo for 5 y = reference
 	
Cohort study:[41]
• **Hip fracture** at a median follow-up of 2.7 y:
  ○ Treatment interruption group: significantly increased risk, adjusted HR = 1.22 (95% CI, 1.11 to 1.34). Risk was 1.8-fold increased after 4 y
  ○ Continued user group: reference
 	
Cohort study:[42]
• **Fracture risk** during the first 6 months after discontinuation:
  ○ Persisting with therapy for greater than 12 months = 60% lower risk (RR = 0.40; *P* = 0.001)
  ○ Discontinuation of therapy within the first 12 months = reference
 	
Combined cohort and case-control study:[39]
• Risk of **AFF** after drug withdrawal = decreased by 70% per year since the last use (OR = 0.28; 95% CI, 0.21 to 0.38)
 	
Cohort and case-control study[35] (Note that results from Schilcher, 2015[35] are also included in the Fink, 2019[20] SR herein):
• **AFF** RR after 4 or more years of use = 126 (95% CI, 55 to 288)
	"[…] the available evidence from prospective and retrospective analyses indicates that treatment cessation is often associated with an increase in fracture risk. From the randomised trial data available, it appears that the strongest predictors of outcome after interrupting therapy are age and BMD at discontinuation."[19] (p.1739)

Table 6: Summary of Findings in Included Health Technology Assessment, Systematic Reviews and Meta-Analysis

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td>

- **AFF** AR after 4 or more years of use = 11 (95% CI, 7 to 14) fractures per 10,000 person-years of use
- Risk of **AFF** after drug withdrawal = decreased by 70% per year since the last use

Cohort study;[36]

- **AFF** incidence after 0.1 to 0.9 years of exposure = 1.78/100,000 persons/year.[a]
- **AFF** incidence after 8 to 9.9 years of exposure = 113.1/100,000 persons/year.[a]

</td><td></td></tr>
<tr><td colspan="2">Fink, 2019[20]</td></tr>
<tr><td>

AEs

Fractures (as a safety endpoint)
(Note that results from Bone, 2004[30] and Tonino, 2000[29] are also included in the Nayak, 2019[21] SR herein.)

<table>
<tr><th rowspan="2">Type of fracture</th><th colspan="2">Relevant Included Studies</th></tr>
<tr><th>ALN 5 mg for 7 y vs.
ALN 10 mg for 7 y vs.
ALN 20 mg for 2 y, then 5 mg for 3 y, then 2 y of placebo.
Tonino, 2000[29]</th><th>ALN 5 mg for 10 y vs.
ALN 10 mg for 10 y vs.
ALN 20 mg for 2 y, then 5 mg for 3 y, then 5 y of placebo.
Bone, 2004[30]</th></tr>
<tr><td>Nonvertebral fracture</td><td>ALN for 7 y (doses combined) vs. placebo:
• No difference (RR = 0.87; 95% CI, 0.40 to 1.91)</td><td>ALN for 10 y (doses combined) vs. placebo:
• No difference (RR = 0.81; 95% CI, 0.38 to 1.71)</td></tr>
<tr><td>Radiographic vertebral fracture</td><td></td><td>ALN for 10 y (doses combined) vs. placebo:
• No difference (RR = 1.40; 95% CI, 0.52 to 3.74)</td></tr>
<tr><td>Clinical vertebral fracture</td><td>ALN for 7 y (doses combined) vs. placebo:
• No difference (RR = 0.92; 95% CI, 0.40 to 2.10)</td><td></td></tr>
</table>

Case-control[38]

- **AFF with radiologic features**, (n = 43 cases): higher risk with current BIS use (HR = 3.36 [95% CI, 1.77 to 11.91] to 5.17 [95% CI, 2.0 to 13.36])

Case-control[43]

- **Subtrochanteric or femoral shaft fracture** diagnosis codes, without radiographic review, (n = 325):
  - Higher risk with current BIS use
    - 3 to 5 y: OR = 1.59 (95% CI, 0.80 to 3.15)
    - Greater than 5 y: OR = 2.74 (95% CI, 1.25 to 6.02)

</td><td>

"Long-term alendronate and zoledronic acid therapies reduce fracture risk in women with osteoporosis. Long-term bisphosphonate treatment may increase risk for rare adverse events, and continuing treatment beyond 3 to 5 years may reduce risk for vertebral fractures."[20] (*p*.37)

"For patients without prior [osteoporosis drug treatment] use, long-term alendronate and zoledronic acid treatments both reduced nonvertebral fractures far more than long-term use of bisphosphonates seems to increase absolute risks of AFF and ONJ."[20] (*p*.47)

</td></tr>
</table>

Table 6: Summary of Findings in Included Health Technology Assessment, Systematic Reviews and Meta-Analysis

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td>RCT[29] (Note that results from Tonino, 2000[29] are also included in the Nayak, 2019[21] SR herein)
• No difference in risk for serious AEs (not defined), between continuation and placebo; RR = 1.05 (95% CI, 0.57 to 1.96)

RCT[30] (Note that results from Bone, 2004[30] are also included in the Nayak, 2019[21] SR herein)
• No difference in risk for serious AEs (not defined), between continuation and placebo; RR = 1.21 (95% CI, 0.75 to 1.96)

Cohort and case-control study[35] (Note that results from Schilcher, 2015[35] are also included in the Dennison, 2019[19] SR herein)
• AFF with radiologic features (n = 172 cases):
○ RR in cohort after 4 or more y of use = 126 (95% CI, 55 to 288)
○ OR in case-control after 3 to 4 y of use = 40 (95% CI, 17 to 91)
○ OR in case-control after 4 to 5 y of use = 116 (95% CI, 58 to 234)
○ OR in case-control after 5 y of use = 93 (95% CI, 66 to 132)</td><td>"However, this evidence is limited to 4 years for alendronate and 6 years for zoledronic acid compared with placebo. In women with prior bisphosphonate treatment, who should have lower risk for subsequent fracture than those without prior treatment, the balance of benefits to harms for continued treatment versus discontinuation is less clear."[20] (p.47)</td></tr>
<tr><td colspan="2">Nayak, 2019[21]</td></tr>
<tr><td><u>Antifracture efficacy in those with osteoporosis (T-score less than or equal to –2.5 SD) at baseline</u>

<table>
<tr><th rowspan="2">Type of fracture</th><th colspan="2">Relevant Included Studies</th></tr>
<tr><th>ZLN for 6 y vs. ZLN for 3 y plus 3 y of placebo. Black, 2012[8]</th><th>ETN for 7 y vs. ETN for 5 y plus 2 y of placebo. Miller, 1997[34]</th></tr>
<tr><td>Femoral Neck</td><td>Incidence:
• 6 y = 9/257 (3.5%)
• 3 y + 3 y placebo = 23/250 (9.2%)
• OR = 0.36 (95% CI, 0.15 to 0.77; P = 0.01)</td><td></td></tr>
<tr><td>Hip</td><td>Total Hip
Incidence:
• 6 y = 5/120 (4.2%)
• 3 y + 3 y placebo = 16/112 (14.3%)
• OR = 0.26 (95% CI, 0.08 to 0.69; P = 0.0113)</td><td></td></tr>
</table>
</td><td>"In conclusion, our findings suggest that it would be reasonable to recommend bisphosphonate discontinuation for women who do not have low hip BMD after 3 to 5 years of initial treatment, while discussing possible continuation of therapy with a bisphosphonate for another 5 years (alendronate) or 3 years (zoledronic acid) for those who do have low hip BMD (e.g., those with T-scores ≤</td></tr>
</table>

Table 6: Summary of Findings in Included Health Technology Assessment, Systematic Reviews and Meta-Analysis

Main Study Findings			Authors' Conclusion
Morphometric vertebral fracture		Years 6 to 7: • 7 y ETN = 2.4% (n = 1/42) • 5 y ETN + 2 y placebo = 10.2% (n = NR)	−2.5) after the initial treatment period."[21] (*p*.719)

BMD Mean Percent Change (95% CI)
(Note that Bone, 2004,[30] and Tonino, 2000[29] are also included in the Eriksen, 2014[22] SR herein. Similarly, Bone, 2004,[30] and Tonino, 2000[29] are also included in the Fink, 2019[20] SR herein)

Location of measurement	Relevant Included Studies		
	ALN 5 mg for 7 y vs. ALN 10 mg for 7 y vs. ALN 20 mg for 2 y, then 5 mg for 3 y, then 2 y of placebo. Tonino, 2000[29]	**ALN 5 mg for 10 y vs. ALN 10 mg for 10 y vs. ALN 20 mg for 2 y, then 5 mg for 3 y, then 5 y of placebo. Bone, 2004[30]**	**ETN for 7 y vs. ETN for 5 y plus 2 y of placebo. Miller, 1997[34]**
Lumbar spine	Years 6 to 7: • Placebo = 0.20 (–0.51 to 0.91) • ALN 5 mg = 1.45 (0.71 to 2.19) • ALN 10 mg = 1.60 (0.92 to 2.28)	Years 6 to 10: • Placebo = 0.3 (–0.8 to 1.5) • ALN 5 mg = 2.5 (1.3 to 3.6) • ALN 10 mg = 3.7 (2.6 to 4.8) Years 8 to 10: • Placebo = 0.2 (–0.7 to 1.1) • ALN 5 mg = 1.2 (0.2 to 2.1) • ALN 10 mg = 2.3 (1.4 to 3.1)	
Spine			End of year 6: • 7 y ETN = 0.5 (–0.44 to 1.44) • 5 y ETN + 2 y placebo = –0.6 (–1.72 to 0.52) End of year 7 • 7 y ETN = 1.8 (0.41 to 3.19) • 5 y ETN + 2 y placebo = 1.4 (–0.78 to 3.58)
Femoral neck	Years 6 to 7: • Placebo = –0.46 (–1.54 to 0.62) • ALN 5 mg = 0.32 (–0.77 to 1.41) • ALN 10 mg = 0.49 (–0.53 to 1.51)	Years 6 to 10: • Placebo = –2.2 (–3.9 to –0.5) • ALN 5 mg = 1.0 (–0.8 to 2.7) • ALN 10 mg = 0.9 (–0.8 to 2.6) Years 8 to 10:	End of year 6: • 7 y ETN = –0.5 (–1.77 to 1.07) • 5 y ETN + 2 y placebo = –0.3 (–1.97 to 1.37) End of year 7

Table 6: Summary of Findings in Included Health Technology Assessment, Systematic Reviews and Meta-Analysis

Main Study Findings				Authors' Conclusion
		• Placebo = –1.7 (–3.0 to –0.3) • ALN 5 mg = 0.3 (–1.2 to 1.7) • ALN 10 mg = 1.0 (–0.3 to 2.4)	• 7 y ETN = 0.5 (–1.11 to 2.11) • 5 y ETN + 2 y placebo = –0.9 (–2.78 to 0.98)	
Trochanter	Years 6 to 7: • Placebo = –0.47 (–1.48 to 0.53) • ALN 5 mg = 0.04 (–0.98 to 1.05) • ALN 10 mg = 0.20 (–0.75 to 1.15)	Years 6 to 10: • Placebo = –1.0 (–2.7 to 0.6) • ALN 5 mg = 0.0 (–1.7 to 1.7) • ALN 10 mg = 1.0 (–0.7 to 2.6) Years 8 to 10: • Placebo = –1.0 (–2.4 to 0.4) • ALN 5 mg = 0.3 (–1.2 to 1.8) • ALN 10 mg = 0.9 (–0.5 to 2.4)	End of year 6: • 7 y ETN = –0.3 (–1.50 to 0.90) • 5 y ETN + 2 y placebo = –1.30 (–2.44 to –0.16) End of year 7 • 7 y ETN = 0.4 (–1.09 to 1.89) • 5 y ETN + 2 y placebo = –0.6 (–2.38 to 1.18)	
Total hip		Years 6 to 10: • Placebo = –1.8 (–3.5 to –0.1) • ALN 5 mg = 0.7 (–0.9 to 2.3) • ALN 10 mg = 0.8 (–0.9 to 2.4) Years 8 to 10: • Placebo = –1.6 (–2.8 to –0.4) • ALN 5 mg = –0.2 (–1.4 to 1.0) • ALN 10 mg = 0.1 (–1.1 to 1.3)		
Total body	Years 6 to 7: • Placebo = –0.50 (–0.95 to –0.04) • ALN 5 mg = –0.29 (–0.76 to 0.17) • ALN 10 mg = 0.35 (–0.08 to 0.78)	Years 6 to 10: • Placebo = –0.6 (–1.7 to 0.4) • ALN 5 mg = –0.7 (–1.8 to 0.3) • ALN 10 mg = 0.4 (–0.6 to 1.4) Years 8 to 10: • Placebo = –0.4 (–1.1 to 0.4) • ALN 5 mg = –0.2 (–0.9 to 0.6) • ALN 10 mg = –0.3 (–1.0 to 0.4)		
Distal third of the forearm	Years 6 to 7: • Placebo = –0.84 (–1.53 to –0.15) • ALN 5 mg = 0.06 (–0.61 to 0.72) • ALN 10 mg = 0.31 (–0.35 to 0.97)	Years 6 to 10: • Placebo = –2.3 (–3.8 to –0.8) • ALN 5 mg = –0.4 (–1.8 to 1.0) • ALN 10 mg = –0.1 (–1.6 to 1.3) Years 8 to 10: • Placebo = –2.1 (–3.2 to –1.1) • ALN 5 mg = –1.1 (–2.1 to –0.1) • ALN 10 mg = –1.0 (–2.0 to 0.1)		

Table 6: Summary of Findings in Included Health Technology Assessment, Systematic Reviews and Meta-Analysis

Main Study Findings				Authors' Conclusion
Distal radius			End of year 6: • 7 y ETN = 0.0 (–2.00 to 2.00) • 5 y ETN + 2 y placebo = 0.5 (–1.66 to 2.66) End of year 7 • 7 y ETN = –1.1 (–3.61 to 1.41) • 5 y ETN + 2 y placebo = 0.2 (–1.64 to 2.04)	

AEs

Meta-analysis of adjusted HRs of **any clinical osteoporotic fracture** (as a safety endpoint)

- Included cohort studies: Adams, 2018[32] and Mignot, 2017[33]
- Summary estimate HR = 1.13 (95% CI, 0.75 to 1.70; I^2 = 94.3%), no significant difference in the risk of any clinical fracture for individuals who discontinued BISs compared with those who continued therapy.[21]

Fractures (as a safety endpoint)
(Note that results from Bone, 2004,[30] Schwartz, 2010,[40] and Tonino, 2000[29] are also included in the Eriksen, 2014.[22] Similarly, results from Bone, 2004,[30] and Tonino, 2000[29] are also included in and the Fink, 2019[20] SR herein, and results from Mignot, 2017[33] and Schwartz, 2010[40] are also included in the Dennison, 2019[19] SR)

Type of fracture	Relevant Included Studies				
	ALN 5 mg for 7 y vs. ALN 10 mg for 7 y vs. ALN 20 mg for 2 y, then 5 mg for 3 y, then 2 y of placebo. Tonino, 2000[29]	**ALN 5 mg for 10 y vs. ALN 10 mg for 10 y vs. ALN 20 mg for 2 y, then 5 mg for 3 y, then 5 y of placebo. Bone, 2004[30]**	**ALN 5 mg for 2 y, then 10 mg for 3y, then 5 mg for 5y vs. ALN 5 mg for 2 y, then 10 mg for 8y vs. ALN 5 mg for 2 y, then 10 mg for 3y, then placebo for 5y. Schwartz, 2010[40]**	**BIS 3 to 5 y + 3 y vs. BIS 3 to 5 y + a drug holiday of 3 y. Mignot, 2017[33]**	**BIS holiday vs. persistent users. Adams, 2018[32]**
Hip				Hip clinical fragility fracture: • Continuation group: n = 2/135 • Drug holiday group: n= 0/31	Holiday group: HR = 0.99 (95% CI, 0.81 to 1.22) Persistent use group: reference

Table 6: Summary of Findings in Included Health Technology Assessment, Systematic Reviews and Meta-Analysis

Main Study Findings						Authors' Conclusion
Nonvertebral	Years 6 to 7: • Placebo = 7.8% (n = 9) • ALN 5 mg = 7.1% (n = 8) • ALN 10 mg = 6.6% (n = 8)	First nonvertebral fracture, years 8 to 10: • Placebo = 12.0% • ALN 5 mg = 11.5% • ALN 10 mg = 8.1%	Fracture risk when t-score measured at femoral neck: • 10 y = 22.6% • 5 y + 5 y placebo = 29.5% • RR = 0.77 (95% CI, 0.50 to 1.2) *P*-value not reported Fracture risk, in those *without* a vertebral fracture at baseline, when: • t-score measured at femoral neck: ○ 10 y = 14.7% ○ 5 y + 5 y placebo = 28.0% ○ RR = 0.50 (95% CI, 0.26 to 0.96) *P*-value not reported • t-score measured at lumbar spine: ○ RR = 0.64 (95% CI, 0.28 to 1.49) *P*-value not reported Fracture risk, in those *with* a vertebral fracture at baseline, when t-score measured at femoral neck: ○ 10 y = 33.3% ○ 5 y + 5 y placebo = 31.6% RR = 1.11 (95% CI, 0.61 to 2.02) *P*-value not reported	Pelvic Clinical Fragility Fracture: • Continuation group: n = 3/135 • Drug holiday group: n = 1/31 Wrist Clinical Fragility Fracture: • Continuation group: n = 3/135 • Drug holiday group: n = 0/31 Foot Clinical Fragility Fracture: • Continuation group: n = 1/135 • Drug holiday group: n = 1/31 Rib Clinical Fragility Fracture: • Continuation group: n = 2/135 • Drug holiday group: n = 0/31 Fibula Clinical Fragility Fracture: • Continuation group: n = 0/135 • Drug holiday group: n = 1/31 Clavicle Clinical Fragility Fracture: • Continuation group: n = 0/135		

Table 6: Summary of Findings in Included Health Technology Assessment, Systematic Reviews and Meta-Analysis

Main Study Findings						Authors' Conclusion
				• Drug holiday group: n = 1/31		
Clinical vertebral fracture	Years 6 to 7: • Placebo = 7.0% (n = 8) • ALN 5 mg = 6.2% (n = 7) • ALN 10 mg = 6.6% (n = 8)		Fracture risk when t-score measured at femoral neck: • 10 y = 4.7% • 5 y + 5 y placebo = 8.3% RR = 0.57 (95% CI, 0.23 to 1.40) *P*-value not reported	Vertebral clinical fragility fracture: • Continuation group: n = 6/135 • Drug holiday group: n = 1/31	Holiday group: HR = 0.82 (95% CI, 0.68 to 1.00) Persistent use group: reference	
Morphometric vertebral fracture		Years 6 to 10: • Placebo = 6.6% • ALN 5 mg = 13.9% • ALN 10 mg = 5.0% • Differences non-significant; *P*-values not reported	Fracture risk, in those *without* a vertebral fracture at baseline, when: • t-score measured at femoral neck: ○ 10 y = 7.7% ○ 5 y + 5 y placebo = 11.0% ○ RR = 0.68 (95% CI, 0.24 to 1.90) *P*-value not reported Fracture risk, in those *with* a vertebral fracture at baseline, when t-score measured at femoral neck: ○ 10 y = 25.4% ○ 5 y + 5 y placebo = 27.5% RR = 0.90 (95% CI, 0.39 to 2.05) *P*-value not reported			
Clinical fractures				Continuation group: 11.9% (n = 16/135) Drug holiday group: 16.1% (n = 5/31); adjusted HR = 1.40 (95% CI, 1.12 to 1.60, *P* = 0.0095)		

Table 6: Summary of Findings in Included Health Technology Assessment, Systematic Reviews and Meta-Analysis

Main Study Findings						Authors' Conclusion
Any osteoporotic fracture					Holiday group: HR = 0.89 (95% CI, 0.79 to 1.01) Persistent use group: reference	

Eriksen, 2014[22]

Mean change in BMD relative to pre-treatment levels
(Note that results from Bone, 2004[30] are also included in the Nayak, 2019[21] and Fink, 2019[20] SRs herein)

Location of measurement	Relevant Included Studies **ALN 5 mg for 10 y vs. ALN 10 mg for 10 y vs. ALN 20 mg for 2 y, then 5 mg for 3 y, then 5 y of placebo. Bone, 2004[30]**
Lumbar spine	• ALN 5 mg for 10 y = 9.3% • ALN 10 mg for 10 y= 13.7% • ALN (mixed doses) for 5 y then placebo for 5 y = 9.3%
Femoral neck	• ALN 5 mg for 10 y = 2.8% • ALN 10 mg for 10 y = 5.4% • ALN (mixed doses) for 5 y then placebo for 5 y = 1.5%
Trochanter	• ALN 5 mg for 10 y = 4.8% • ALN 10 mg for 10 y = 10.3% • ALN (mixed doses) for 5 y then placebo for 5 y = 5.3%
Total hip	• ALN 5 mg for 10 y = 2.6% • ALN 10 mg for 10 y = 6.7% • ALN (mixed doses) for 5 y then placebo for 5 y = 3.4%
Total body	• ALN (mixed doses) for 5 y then placebo for 5 y = BMD remained significantly above the original study baseline (*P*-value not reported)
Distal third of the forearm	• ALN (mixed doses) for 5 y then placebo for 5 y = decreased BMD (values not reported)

"No unexpected AEs emerging from long-term treatment were identified in these studies and the long-term tolerability profiles of bisphosphonates remain favorable. Data from the two withdrawal extension studies of alendronate and zoledronic acid have also demonstrated residual fracture benefits in patients who discontinued treatment for 3 to 5 years. It has been suggested that patients at high risk of fracture who have low BMD (T-score <−2.5) and/or an incident vertebral fractures after 3 to 5 years of treatment may benefit most from continuation of bisphosphonates. On the other hand, treatment

Table 6: Summary of Findings in Included Health Technology Assessment, Systematic Reviews and Meta-Analysis

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td>

Bone turnover markers

RCT[30] (Note that results from Bone, 2004,[30] are also included in the Nayak, 2019[21] and Fink, 2019[20] SR herein)

- ALN 5 mg or 10 mg continuation group = maintained their reduction
- Placebo group = "small increases in [bone turnover marker] levels (including [bone-specific alkaline phosphatase]) that were still below the pretreatment values at the end of the extension period"[22] (*p.*131) (no effect estimates or statistics provided).

AEs

Fractures (as a safety endpoint)

(Note that results from Schwartz, 2010,[40] are also included in the Nayak, 2019[21] and the Dennison, 2019[19] SR herein)

<table>
<tr><th rowspan="2">Type of fracture</th><th>Relevant Included Studies</th></tr>
<tr><th>ALN 5 mg for 2 y, then 10 mg for 3 y, then 5 mg for 5 y vs.
ALN 5 mg for 2 y, then 10 mg for 8 y vs.
ALN 5 mg for 2 y, then 10 mg for 3 y, then placebo for 5 y; a secondary analysis.
Schwartz, 2010[40]</th></tr>
<tr><td>Nonvertebral</td><td>• ALN for 10 y: RR = 0.50 (95% CI, 0.26 to 0.96)
• ALN for 5 y plus 5 y of placebo: reference</td></tr>
</table>

Fracture (as a safety endpoint), secondary analysis of HORIZON-PFT[44]:

- "[…]total hip or femoral neck BMD of ≤2.5, and incident morphometric vertebral fracture during the 3 years of zoledronic acid treatment were significantly associated with new morphometric vertebral fractures in the subsequent 3 years (*P* = 0.008, *P* = 0.0007, and *P* = 0.0156 respectively)".[22] (*p.*129)

RCT[29] (Note that results from Tonino, 2000[29] are also included in the Nayak, 2019[21] and Fink, 2019[20] SR herein)

- Incidence of AEs:
  - No significant difference between groups
- Upper gastrointestinal AEs:
  - No significant difference between groups
- Serious AEs:
  - No significant difference between groups
- Discontinuation due to AEs:
  - No significant difference between groups

RCT[30] (Note that results from Bone, 2004,[30] are also included in the Nayak, 2019[21] and Fink, 2019[20] SR herein)

- Death:
  - ALN 5 mg or 10 mg continuation group = 4 deaths (none considered associated with ALN treatment)

</td><td>discontinuation may be considered for patients at low risk for fracture who have achieved a BMD T-score <−2.5 after 3 to 5 years of treatment. Fracture risk assessments should be conducted regularly to determine whether treatment could be stopped or whether it should be reinitiated. The duration of treatment and possible discontinuation of treatment should be personalized for individual patients based on their response to treatment, fracture risk and comorbidities. Although comparable data in men are lacking, there are no reasons to suggest a different therapeutic strategy in male osteoporosis."[22] (*p.*134)</td></tr>
</table>

Table 6: Summary of Findings in Included Health Technology Assessment, Systematic Reviews and Meta-Analysis

Main Study Findings	Authors' Conclusion
○ Placebo group: NR • Incidence of AEs: ○ No significant difference between groups • Upper gastrointestinal AEs: ○ No significant difference between groups • Serious AEs: ○ No significant difference between groups • Discontinuation due to AEs: ○ No significant difference between groups	

AE = adverse event; AFF = atypical femoral fractures; ALN = alendronate; AR = absolute risk; BIS = bisphosphonate; BMD = bone mineral density; CI = confidence interval; ETN = etidronate; FLEX = Fracture Interventional Trial Long Term Extension; HORIZON-PFT = Health Outcomes and Reduced Incidence with Zoledronate Once Yearly – Pivotal Fracture Trial; HR = hazard ratio; NR = not reported; ONJ = osteonecrosis of the jaw; OR = odds ratio; RR = relative risk; SD = standard deviation; SR = systematic review; ZLN = zoledronic acid.

Note:

[a] A discrepancy was noted between the result reported in the SR, described as: "Dell using radiographic review of claims data found a rate of AFF of 2/100,000 after 2 years of exposure and 78/100,000 after 8 years of exposure"[19] (*p*.1738) and the result reported in the referenced primary article.[36] The values from the primary articles were reported in this table. The reader is cautioned that, in general, primary studies of SRs are not re-evaluated.

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
American College of Physicians, 2017[23]	
1. "Recommendation 2: ACP recommends that clinicians treat osteoporotic women with pharmacologic therapy for 5 years."[23] (*p*.818)	1. Grade: weak recommendation; low-quality evidence
European Menopause and Andropause Society, 2017[24]	
1. "Decisions should be individualized, taking into consideration the long-term efficacy of bisphosphonates and denosumab, their safety, and the fracture risk of the specific patient."[24] (*p*.28) 2. "Discontinuation of bisphosphonates should be considered in all patients who have been treated for more than five years with alendronate or more than three years with risedronate or zoledronic acid."[24] (*p*.28) **3.** "Patients should be re-evaluated 1-3 years after bisphosphonate discontinuation. The decision to resume treatment depends on the presence of new fractures, risk factors and possibly bone mineral density."[24] (*p*.28)	(Not reported)
National Osteoporosis Guideline Group, 2017[25]	
Postmenopausal women: 1. "Continuation of bisphosphonate treatment beyond 3-5 years (3 years for zoledronic acid and 5 years for alendronate, ibandronate and risedronate) can generally be recommended in the following situations: a. age 75 years or more b. previous history of a hip or vertebral fracture c. occurrence of one or more low trauma fractures during treatment, after exclusion of poor adherence to treatment (for example less than 80% of treatment has been taken) and after causes of secondary osteoporosis have been excluded d. current treatment with oral glucocorticoids =7.5 mg prednisolone/day or equivalent"[25] (*p*.17) 2. "If treatment is discontinued, fracture risk should be reassessed after a new fracture, regardless of when this occurs. If no new fracture occurs, assessment of fracture risk should be performed again after 18 months to 3 years."[25] (p.17) 3. "Treatment review should be performed after 5 years of treatment with alendronate, risedronate or ibandronate and after 3 years of treatment with zoledronic acid a. Reassessment of fracture risk in treated individuals can be performed using FRAX with femoral neck BMD b. If biochemical markers of bone turnover indicate relapse from suppressed bone turnover and BMD has decreased following withdrawal, resumption of treatment should be considered c. "There is no evidence to guide decisions beyond 10 years of treatment and management options in such	1. Evidence level IIb, Grade of recommendation B 2. Grade C recommendation 3. Grade C recommendation a. Grade B recommendation b. Grade C recommendation

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
patients should be considered on an individual basis".[25] (*p*.17)	
Royal Australian College of General Practitioners, 2017[26]	
1. "Reconsider the need to continue bisphosphonate therapy after 5–10 years in postmenopausal women and men over 50 years of age with osteoporosis who have responded well to treatment (T-score ≥–2.5 and no recent fractures). If BMD remains low (T-score ≤–2.5) and/or there are incident vertebral fractures, continue treatment. Treatment should be restarted if there is evidence of bone loss, especially at the hip, or if a further minimal trauma fracture is sustained."[26] (*p*.IV) 2. "Regularly re-assess fracture risk and requirement for anti-osteoporotic therapy in patients who are not receiving therapy but remain at increased risk of fracture."[26] (*p*.V) 3. "Review all patients 3–6 months after initiating a specific pharmacological intervention for osteoporosis, and annually thereafter. BMD testing at the 3–6 month review is not indicated." [26] (*p*.V)	1. Grade D recommendation 2. Grade B recommendation 3. Grade B recommendation
Spanish Society for Research on Bone and Mineral Metabolism, 2015[27]	
1. "Treatment should last as long as necessary to decrease the risk of fractures to acceptable levels. Although there is no one official definition of what is considered an acceptable level, it has been suggested that a BMD > -2.5 T in patients with no fractures or > -2 T in patients with 1 previous fracture (more than 3-5 years) could be an acceptable level."[27] (*p*.521) 2. "The achievement of objectives should be assessed every 3-5 years. If the goals are considered achieved, the treatment may be discontinued."[27] (*p*.521)	1. Grade D recommendation 2. Grade D recommendation
Winnipeg Regional Health Authority, 2014, Canada[6]	
1. "Recommendation: Individuals at high risk for fracture should continue osteoporosis therapy without a drug holiday."[6] (*p*.9) 2. "Individuals at Moderate Risk who have been prescribed pharmacologic therapy should be reassessed every 3-5 years regarding the need for ongoing medication or consideration of a drug holiday or for drug discontinuation."[6] (*p*.9)	1. Grade D recommendation 2. Not reported

ACP = American College of Physicians; BMD = bone mineral density; FRAX = tool to evaluate fracture risk of patients.

Appendix 5: Overlap between Included Systematic Reviews

Table 8: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation				
	Dennison, 2019[19]	Fink, 2019[20]	Nayak, 2019[21]	Davis, 2016[18]	Eriksen, 2014[22]
Adams, 2018[32]			X		
Black, 2006[7]			X		
Black, 2012[8]			X		X
Bone, 2004[30]		X	X		X
Cosman, 2011[44]					X
Curtis, 2018[41]	X				
Dell, 2012[36]	X				
Khow, 2017[37]	X				
Koh, 2017[38]		X			
Mignot, 2017[33]	X		X		
Miller, 1997[34]			X		
Park-Wyllie, 2011[43]		X			
Schilcher, 2011[39]	X				
Schilcher, 2015[35]	X	X			
Schwartz, 2010[40]	X		X		X
Ström, 2015[42]	X				
Tonino, 2000[29]		X	X		X

Appendix 6: Additional References of Potential Interest

Clinical Practice Guidelines

Unclear Methodology

Best Practice Advocacy Centre New Zealand. Bisphosphonates: addressing the duration conundrum. Dunedin (NZ): bpac^{nz}; 2019: https://bpac.org.nz/2019/docs/bisphosphonates.pdf. Accessed 2019 Oct 4.
See: Determining an appropriate duration of bisphosphonate use

Kaiser Permanente Guideline Oversight Group. Osteoporosis screening, diagnosis, and treatment guideline. Seattle (WA): Kaiser Foundation Health Plan of Washington; 2019: https://wa.kaiserpermanente.org/static/pdf/public/guidelines/osteoporosis.pdf. Accessed 2019 Oct 4.
See: Recommended pharmacologic options

Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2016 Jan;31(1):16-35.
PubMed: PM26350171

Toward Optimized Practice (TOP) Osteoporosis CPG Committee. Diagnosis and management of osteoporosis: clinical practice guideline. Edmonton (AB): TOP; 2016 Feb: http://www.topalbertadoctors.org/download/1907/Osteoporosis%20CPG.pdf. Accessed 2019 Oct 4.
See: DISCONTINUING BISPHOSPHONATE THERAPY

Position Statements

Simm PJ, Biggin A, Zacharin MR, et al. Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. *J Paediatr Child Health*. 2018 Mar;54(3):223-233:
PubMed: PM29504223

Meier C, Uebelhart B, Aubry-Rozier B, et al. Osteoporosis drug treatment: duration and management after discontinuation. A position statement from the SVGO/ASCO. *Swiss Med Wkly*. 2017;147:w14484.
PubMed: PM28871570

Lee SH, Gong HS, Kim TH, et al. Position statement: drug holiday in osteoporosis treatment with bisphosphonates in South Korea. *J Bone Metab*. 2015 Nov;22(4):167-174.
PubMed: PM26713307