Comparative Effectiveness Review Disposition of Public Reviewer Comments Report

Research Review Title: Long-term Drug Therapy and Drug Holidays for Osteoporosis Fracture Prevention: A Systematic Review

Draft review available for public comment from October 30, 2018 to November 27, 2018.

Research Review Citation: Fink HA, MacDonald R, Forte ML, Rosebush CE, Ensrud KE, Schousboe JT, Nelson VA, Ullman K, Butler M, Olson CM, Taylor BC, Brasure M, Wilt TJ. Long-Term Drug Therapy and Drug Holidays for Osteoporosis Fracture Prevention: A Systematic Review. Comparative Effectiveness Review No. 218. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2015-00008-I) AHRQ Publication No. 19-EHC016-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2019. DOI: https://doi.org/10.23970/AHRQEPCCER218

Comments to Research Review

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The tables below include the responses by the authors of the review to each submitted peer reviewer comment. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality. After revision of the draft report to address peer reviewer comments, a revised report was posted for public comments for a 3-4 week period.

Comments on draft reviews and the authors' responses to the peer review and public comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

Section	Commentator & Affiliation	Comment	Response
Executive Summary	Public Commenter #1 (Rafael Pirtillo Ferman -Altietus College)	We need more information number of cases in prevention and outcomes and number of patients under treatment	Thank you for your comment. Because of space limitations, we added this information to the discussion of the report and evidence summary.
Introduction	Public Commenter #6 (Jason Spangler & George Jarekso-Amgen)	Page 3 (Table 1), Page 8 (Table 3), Page 10 (Table 4), Page 17 (Table 5) Comment: Table 4 defines the interventions to be included in this systematic review as "Drugs FDA approved for osteoporosis treatment or prevention" but then includes the anti-sclerostin monoclonal antibody, romosozumab, which is not currently FDA approved. The Draft Report notes that romosozumab will only be included in this review if FDA approval is received before the close of the Draft Report comment period. Given that FDA approval is not anticipated until after the close of the comment period, romosozumab should be removed as an intervention throughout (applies to Tables 1, 4, and 5). In addition, Amgen does not consider it appropriate to list anti-sclerostin monoclonal antibody class-specific harms in Table 3 when the final prescribing information for romosozumab is not yet available. Since there are no FDA approved treatments within the anti-sclerostin monoclonal antibody class, Amgen recommends that this class should be removed from the Draft Report throughout.	Thank you for the comment, Romosozumab has been removed from our report.

Section	Commentator & Affiliation	Comment	Response
Introduction	Public Commenter #6 (Jason Spangler & George Jarekso-Amgen)	Page 8 (Table 3) Comment: Table 3 currently lists several harms as class-specific harms for DMB. The basis for inclusion of these harms for DMB is not immediately apparent. For example, heart attacks and esophageal cancer are not listed in the Prolia® FDA-approved product labeling nor is there any discussion of studies suggesting an association of these harms with DMB in this draft comparative effectiveness review. With regards to upper gastrointestinal (GI) AEs, data are limited and a causal relationship to DMB exposure has not been established as compared to those that have been observed with oral bisphosphonate use.1 Further, the upper GI related AEs associated with Prolia as presented in the USPI differ from those described in product labeling for other osteoporosis treatments, especially for the oral bisphosphonates.1 We are concerned that the current specified list of class-specific harms for DMB can be misinterpreted without additional clarification. For these reasons, we propose that the Agency reconsider the presentation of Table 3 by providing the references for each listed harm or to align them more closely to the Prolia® USPI. [1]Amgen Inc. 2018. Prolia (denosumab) U.S. Prescribing Information, (06/2018). Cummings SR, Ferrari S, Eastell R *et al.*	The list of harms in Table 3 was generated by NIH and AHRQ, and refined based on NIH, Key Informants, and Technical Expert Panel harms research priorities. We were charged to evaluate the literature to determine whether these harms were associated with long-term treatment with these osteoporosis drugs. Because the draft heading and a subheading of table 3 could have suggested that all the listed harms were associated with these osteoporosis drug classes, we changed them as follows: 'Harms evaluated for possible association with long-term osteoporosis drug therapy' and 'Harms outcomes evaluated.' We also changed the way table 2 referred to table 3 so that it didn't imply that all the listed harms were associated with these treatments.
Methods	Public Commenter #8 (ODP/P2P panel)	The panel questioned the exclusion of studies that were exactly 3 years in length (example: the FREEDOM Trial). They expressed concerns about the scope of the review given that a couple of these trials were excluded but seemed relevant.	The evidence team, AHRQ, NIH, and Key Informants extensively discussed this during protocol development. The rationale for the threshold of >3 years is that multiple RCTs have shown that multiple agents reduce risk of osteoporotic fractures up to 3 years. The evidence on the efficacy of trials of 3 years or shorter was reviewed in a prior AHRQ review.(Crandall Ann Int Med 2014, Qaseem Ann Int Med 2017) Therefore, we were asked to not focus on these shorter trials, but to evaluate the evidence about the efficacy and harms of treatment longer than 3 years. We explained this rationale in the introduction to the report and . We revised the report to remind the readers of this focus of the report in the discussion.

Section	Commentator & Affiliation	Comment	Response
Results	Public Commenter #6 (Jason Spangler & George Jarekso-Amgen)	Page 24 (Key Points on Key Question1) Comment: Page 24 of the Draft Report states "In postmenopausal women with BMD T score < 1.8, there was no difference between denosumab therapy for 4 years versus placebo in risk for incident clinical fracture (low SOE)." However, this statement is based on data from a small phase 2 study that was not designed or powered to assess differences in fracture rates.2 The study was initially designed as a 2-year dose-ranging study comparing DMB with placebo, and then extended to collect efficacy (BMD and bone turnover markers) and safety data up to 4 years. Consequently, many patients did not receive the licensed DMB dose for either all or part of the study. Fractures were not prespecified as an outcome and were captured via routine adverse event reporting. Importantly, fracture data were presented for all DMB patients combined, regardless of treatment duration, and therefore included a mixture of patients with short- and long-term treatment. This is noted on page 25 of the Draft Report and leads to the Agency conclusion on page ES-3 "It was not possible to directly compare fracture risk between women on long-term denosumab versus placebo, because fracture results for long-term denosumab and denosumab discontinuation treatment arms were pooled." This is consistent with the Agency discussion on page ES-13 which states "we found no usable data about the long-term efficacy of other agents for reducing fracture risk versus placebo." Amgen agrees with the statements on pages ES-3 and ES-13 that it is not possible to compare fracture risk for long-term DMB therapy versus placebo from this study, and requests that the page 24 statement is revised accordingly (i.e., removal of "no difference between denosumab therapy for 4 years versus placebo" wording). [2]Miller PD, Bolognese MA, Lewiecki EM *et al*. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone* 2008;43:222-229.	In re-evaluating the evidence from this phase 2 trial on long-term fracture prevention for denosumab versus placebo, we agree with the reviewer that the statement 'low strength evidence for no difference in risk of incident clinical fracture' should be changed to 'insufficient evidence to draw conclusions about any differences between long-term denosumab and placebo.' We added a bullet to the key messages at the start of the report stating: "No eligible trial provided usable data about whether long-term denosumab reduces risk of incident fractures." We modified Table A in the evidence summary to indicate that for long-term denosumab versus placebo, the evidence about the risk of incident clinical fractures is insufficient. The narrative of the evidence summary already stated that it wasn't possible to directly compare fracture risk between long-term denosumab and placebo using data from this single eligible trial, and we left this unchanged.

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Results	Public Commenter #4 (Arthur Santora-Enter Bio, Ltd.)	Statements about the risk of potential adverse drug reactions are made without the rigor that is applied to statements made about fracture risk reduction. For example, on page ES-1, in the 4th paragraph the following statement appears: "Short-term RCTs **and** observational studies have found that oral bisphosphonates increase upper gastrointestinal (GI) symptoms; bisphosphonates and denosumab are associated with rare atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ)." However, RCTs have not indicated that either AFF or ONJ occur at increased risk; only observational studies suggest increased risk. Moreover, the limitations of the observational studies of ONJ are minimized. For example, the only observational study rated as having a Low SOE did not actually report the risk of ONJ. "inflammatory Jaw Events" were the outcome of interest (Reference 45 in the Draft). No observational study data are cited to support a conclusion that the risk of ONJ is related to duration of prior therapy with a bisphosphonate or denosumab, or that the risk of ONJ does or does not diminish during a Drug Holiday. The possibility that failure to treat during a "drug holiday" may result in "harms" should part of the benefit/"harms" discussion.	The reviewer is correct about the statement he references on page ES-1. Attempting to concisely summarize the short-term data, we erroneously conflated information from RCTs with that from observational studies. We corrected this issue in the revised introduction. The reviewer is correct in that the draft report provided limited detail on the methodological limitations of the ONJ observational studies. This is evident when compared to the detail provided about the methodological limitations of the AFF observational studies. We provided additional details about the limitations of the ONJ observational studies in the discussion of the revised report. The draft report did not state that risk of ONJ was related to duration of bisphosphonate or denosumab therapy. The draft report stated that evidence was insufficient to draw conclusions about differences in risk of ONJ between alendronate continuation versus discontinuation, risk of ONJ between zoledronate continuation versus discontinuation, and risk of any harms between denosumab continuation and discontinuation. Because the trials that compared drug continuation with discontinuation were framed using discontinuation as the reference group and reported on whether fracture risk was reduced with continued treatment, we didn't frame the occurrence of fractures after discontinuation as a possible harm of drug holidays.

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Results	Public Commenter #4 (Arthur Santora-Enter Bio, Ltd.)	While most of the tabular data are well supported in the narrative review, Table 3. Class-Specific Harms of Drugs Used for Osteoporosis Treatment has several important errors. Atrial fibrillation has been associated with intravenous zoledronic acid and not with either oral bisphosphonates or denosumab. An increased risk of heart attacks has not been associated with any bisphosphonates or with denosumab. Upper GI intolerance has been associated with oral bisphosphonates but not with intravenous bisphosphonates or denosumab. Esophageal cancer is not a class specific adverse drug reaction for either bisphosphonates or denosumab. While estrogen has been associated with both breast and endometrial cancer, its use may be associated with reduced (not increased) colon cancer risk. PTH and PTHrP analogs are associated with osteosarcoma in rat carcinogenicity studies, although risk has not been confirmed in humans. It is premature to describe class-specific harms of antisclerostin antibody therapy. I suggest that the committee carefully review the FDA-approved Prescribing Information for each product prior to revising this table.	The list of harms in Table 3 was generated by NIH and AHRQ, and refined based on NIH, Key Informants, and Technical Expert Panel harms research priorities. We were charged to evaluate the literature to determine whether these harms were associated with long-term treatment with these osteoporosis drugs. Because the draft heading and a subheading of table 3 could have suggested that all the listed harms were associated with these osteoporosis drug classes, we changed them as follows: 'Harms evaluated for possible association with long-term osteoporosis drug therapy' and 'Harms outcomes evaluated.' We also changed the way table 2 referred to table 3 so that it didn't imply that all the listed harms were associated with these treatments.
Results	Public Commenter #1 (Rafael Pirtillo Ferman -Altietus College)	Drugs still working	Thank you for the comment.
Results	Public Commenter #7 (ASBMR)	Drug holidays section is confusing in terms of dissecting out benefits versus harms. The "harm" of an incident osteoporotic fracture during a drug holiday is not really discussed.	Thank you. We considered reporting the results of drug holiday studies as the effect of drug discontinuation versus the reference group of drug continuation, with incident fractures as a harm. However, all eligible drug holiday studies considered the continuation the intervention and the discontinuation the reference group, and reported on prevention of incident fractures as a benefit. Flipping the reference group would have required us to reverse all the results from the way the trials were framed and reported, and we were concerned it would be confusing to many readers who were familiar with the primary trial data.

Section	Commentator & Affiliation	Comment	Response
Results	Public Commenter #1 (Rafael Pirtillo Ferman -Altietus College)	Drugs has to be monitoring	Thank you for the comment.
Results	Public Commenter #7 (ASBMR)	Mentioning AFF and ONJ together implies that the research questions are the same for each. They are not.	The research questions for this review focused on risk of harms associated with long-term osteoporosis drug treatment. We looked for evidence about a list of possible harms, and reported results about the association of treatments with these harms separately. In summarizing our findings in key points and key messages, we sometimes consolidated results for readability, though not when doing so would have inappropriately conflated the results.

Section	Commentator & Affiliation	Comment	Response
Results	Public Commenter #6 (Jason Spangler & George Jarekso-Amgen)	Page 76 (Key Points on Key Questions 7 and 8) Comment: The Draft Report states "In postmenopausal women with osteoporosis or osteopenia, between denosumab continuation and discontinuation (placebo drug holiday), evidence was insufficient to draw conclusions about differences in risk of harms" and "we identified no evidence about whether differences in risk of harms between denosumab continuation and discontinuation vary as a function of patient, bone or drug characteristics." While these statements are correct based on the key DMB study identified, the incidence of multiple vertebral fractures has been observed to increase following DMB discontinuation, with higher event rates in patients with a history of vertebral fracture.2,4,6 Therefore, while drug holidays may be an option for certain osteoporosis therapies, this is not the case for DMB. Patients should be advised not to interrupt DMB therapy without first talking to their physician.1 Further, if DMB is discontinued, physicians should consider transition to another antiresorptive agent.1,4,5 [1]Amgen Inc. 2018. Prolia (denosumab) U.S. Prescribing Information, (06/2018). [2]Miller PD, Bolognese MA, Lewiecki EM *et al.* Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone* 2008;43:222-229. [4]Cummings SR, Ferrari S, Eastell R *et al.* Vertebral fractures after discontinuation of denosumab: A post hoc analysis of the randomized placebo-controlled FREEDOM Trial and its extension. *J Bone Miner Res* 2018;33:190-198. [5]Tsourdi E, Zillikens MC. Certainties and Uncertainties About Denosumab Discontinuation. *Calcif Tissue Int* 2018;103:1-4. [6]Brown JP, Roux C, Torring O *et al.* Discontinuation of denosumab and associated fracture incidence: analysis from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial. *J Bone Miner Res* 2013;28:746-52.	Thank you for your comment. In the report introduction, after the statement about the lack of consensus about bisphosphonate drug holidays (e.g., who should get them, when they should start and end, how they should be monitored, etc.), we added new language stating: "Drug holidays are not recommended after denosumab therapy because of post-hoc data indicating rapid bone loss after denosumab discontinuation and a possible small post-treatment increase in risk of multiple radiographic vertebral fractures.(Cummings JBMR 2018) In the discussion, informed by Tsourdi and Zillikens (CTI 2018), we recommended several related lines of future research to investigate risk for post-denosumab fractures and the efficacy and harms of different alternatives for post-denosumab treatment.

Section	Commentator & Affiliation	Comment	Response
Discussion	Public Commenter #3 (Juliet Compstock-Cambridge School of Medicine)	(Page 8) Here and elsewhere in the document the benefit/risk balance of HT is oversimplified. The narrative does not acknowledge the age dependence of effects on coronary artery disease risk in women aged 50-60 yrs (no significant increase (combined) or no effect or decrease (E only)), nor does it distinguish between unopposed and opposed estrogen therapy when discussing the risk of breast cancer.	We revised the section of the report on harms associated with long-term hormone therapy to add substantial data about possible variation in various harms as a function of a long list of patient characteristics. With respect to coronary heart disease, newly inserted language includes: "In the WHI trial that compared estrogen versus placebo (Anderson JAMA 2004), the association of treatment assignment with risk of coronary heart disease…did not significantly differ by age…" Though the HRs appeared to trend towards a reduced risk in women 50-59 years old compared to no difference in risk in women 60-69 and 70-79, the p-value for interaction by age category was not significant. Undoubtedly, the test for interaction had low power, but also the authors performed many tests for significance in this paper and did not adjust for multiple comparisons. Our revised hormone therapy harms section also reads: "In the WHI trial that compared estrogen plus progestin versus placebo, the association of treatment group with risk of coronary heart disease, stroke, or venous thromboembolism did not significantly differ by age,…"
Discussion	Public Commenter #8 (ODP/P2P panel)	The panel commented that the lack of inclusion of sequencing studies (ie, use of anabolic agents) is a limitation of the review.	Our evidence team agrees and included this limitation in the draft report. This limitation remains in the final report.
Discussion	Public Commenter #8 (ODP/P2P panel)	Another limitation is that Teriparatide and Abaloparatide weren't covered because all studies less than 3 years.	Our evidence team agrees. Because all trials of teriparatide and abaloparatide were less than 3 years in duration (and because product labeling recommends against lifetime use of these agents for more than 2 years), the long-term benefits and harms of these agents in patients with osteoporosis is unknown. We added this point to the limitations section of the report discussion.

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Discussion	Public Commenter #7 (ASBMR)	Surprised that the Efficacy of Short-term Treatment section focuses on screening data that excluded women with fractures, especially since there is strong and consistent data on efficacy. Sentence should be added which prominently relays the fact that the data that excluded women with fractures were the basis of the information for this section.	Our review did not evaluate and does not include a section on the efficacy of short-term osteoporosis drug treatment. Our comments in the introduction about evidence on the efficacy of short-term osteoporosis drug treatment were largely based on a prior AHRQ review (Crandall Ann Intern Med 2014, Qaseem Ann Intern Med 2017) which did not focus on studies of women without fractures. The AHRQ review for the USPSTF recently completed by UNC-RTI focused on osteoporosis drug treatment efficacy in participants without fractures. However, there is no connection between that review and the current review, other than that results from both were presented at the recent NIH ODP P2P Workshop.
Discussion	Public Commenter #7 (ASBMR)	Evidence review of efficacy of short-term treatment – defined as three years (zoledronate) to five years (alendronate) of bisphosphonates – should make case that there are several options for efficacious prescriptions that prevent fractures after 3-5 years of treatment.	A review of the evidence on short-term treatment was outside the scope of this review. Limited information about short-term efficacy was included in the introduction to provide context for this review about long-term treatment and drug holidays. Evidence that short-term treatment is effective for fracture prevention is not sufficient to make the case that there several effective drug treatment options for "after" 3-5 years of treatment.
Discussion	Public Commenter #7 (ASBMR)	The recommendations regarding future research should prominently highlight the need for further studies related to treatment with denosumab, in particular offset effect patterns, discontinuation of treatment (e.g. which bisphosphonate, dosage, etc.) and treatment of patients with multiple vertebral fractures.	The section on future research recommendations was revised to include recommendations for research to investigate risk for post-denosumab fractures and the efficacy and harms of different alternatives for post-denosumab treatment.

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Discussion	Public Commenter #7 (ASBMR)	Report should include a discussion on the relative risk of osteoporotic fractures and very rare side effects. Current draft comes across that the lack of evidence for fracture reduction across the board with long-term treatment is completely counterbalanced by the side effects, and this is clearly far from proven.	We believe the reviewer's statement mischaracterizes the draft report discussion, which stated: "In patients who already have completed a course of osteoporosis drug treatment (i.e., 3 to 5 years), the most favorable trial evidence for continued treatment is for an approximately 3 percent absolute reduction in risk of incident clinical vertebral fractures with 10 years of alendronate versus 5 years. Observational data suggests that the absolute increases in risk for AFF and ONJ with long-term bisphosphonate treatment are far smaller." Because of substantial differences in the study designs from which the fracture reduction and AFF and ONJ risk estimates were derived, we elected to not estimate a ratio of these events in patients on long-term treatment compared to no bisphosphonate treatment.
Discussion	Public Commenter #7 (ASBMR)	The discussion around efficacy in osteoporosis and osteopenia seems a little outdated and is really based on the alendronate data. There is clearly great potential danger in subgroup analyses in trials, and analyses using a continuous approach have suggested less evidence for differences in efficacy by BMD. Group should consider the evidence from the Reid trial of zoledronic acid in osteopenia (DOI:10.1056/NEJMoa1808082).	As the reviewer suggests, the discussion around efficacy as a function of BMD was informed by the alendronate data, in which subgroup analyses defined by osteoporosis and osteopenia cutpoints were specified before data was unblinded. The Reid zoledronate trial was published after the publically posted version of our report was submitted. However, it has been incorporated in this final report. It is unknown whether results from the Reid zoledronate trial are generalizable to treatment of osteopenic patients with other osteoporotic drugs.

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Discussion	Public Commenter #5 (Karen Friday-International Society for Clinical Densitometry)	We would also emphasize the need for the use of DXA in future research of long-term bone anti-resorption or anabolic bone therapy, discontinuation of osteoporosis drugs or in evaluation of atypical femur fractures.	The revised Discussion section on future research needs states: "Future…studies should specify analysis plans a priori to investigate possible effect modifiers of both benefits and harms of long-term therapy and drug holiday outcomes. Among other factors, these should include age, and both BMD and bone markers before and during treatment or drug holidays. Results of patient-level data from osteoporosis drug trials on the association of early treatment changes in BMD and bone turnover markers with risk of incident fractures may improve understanding of the potential and limitations of these measures as surrogates for incident fracture."
Discussion	Public Commenter #4 (Arthur Santora-Enter Bio, Ltd.)	The Research Needs presented on ES-16 are thoughtful and focus on the need to carefully evaluate the benefits and risks of discontinuation of therapy after 3 to 5 years of treatment with a bisphosphonate. However, it is unrealistic to consider a new long-term placebo-controlled, fracture end point trial that enrolls either osteoporotic men or other populations of osteoporotic women who were under-represented in prior studies (e.g., African-Americans, Asian-Americans or those with multiple co-morbid conditions) as IRBs would not approve such a study for ethical reasons and potential subjects would not want to participate. Consider re-wording the recommendation that, "Future studies should systemically collect and report harms data." In a clinical trial all adverse events are collected without regard to the investigator's assessment of causality. Analysis of an unbiased collection of all adverse event data are required to determine whether an intervention is associated with a higher (harm) or lower (benefit) risk of a specific adverse event.	We understand there are numerous challenges to conducting new, long-term, placebo-controlled, fracture endpoint trials. However, the generalizability of published trials to excluded populations remains uncertain, and BMD and bone markers are not yet established surrogates. In addition to RCTs, observational studies that are carefully designed to minimize bias will be necessary to address many clinical questions. We appreciate the reviewer's explanation about how harms are collected in trials. Nevertheless, reporting of harms in trials appeared neither uniform nor complete. When harms are reported in this way, we are unable to assume they were systematically collected. We agree with the reviewer's recommendation for how trial harms should be reported. We changed the wording to: "Future studies should systematically collect, analyze and report harms data."
General	Public Commenter #1 (Rafael Pirtillo Ferman -Altietus College)	Dr Gil has a good point how he has been training the personal before pass yo the physician mention prevention is number one and saving money or reduce budgets in healthcare	Thank you for the comment.

Section	Commentator & Affiliation	Comment	Response
General	Public Commenter #2 (Anonymous)	Excellent evidence-based review with good adherence to the KQs and rigorous unbiased approach to answering important questions. I have no criticism to offer and I do not have any conflicts of interest with regard to the research team or topic.	Thank you for the comment.
General	Public Commenter #3 (Juliet Compstock-Cambridge School of Medicine)	On page 2 under Key Messages:- A section on denosumab should be included.- Eighth bullet point a causal relationship between long-term bisphosphonate therapy and AFFs is accepted, therefore replace may increase with increases. The same applies to the Results section on page viii.- Ninth bullet point suggest adding oldest old and frail in the diverse populations.- Tenth bullet point suggest replacing standard with universally agreed. Other:- Page 36, last paragraph: Abaloparatide should be included in text (it is included in Table 1).- Page 118, HT is not included in the section on harms of long-term osteoporosis therapy.	A key message was added that indicated that evidence was insufficient about whether long-term denosumab lowered risk of fractures. 'May increase' was selected to best reflect the low strength of the evidence on risk of AFFs identified for this systematic review (i.e., long term trials and long term controlled observational studies). As suggested, we added frail and oldest old to the list of populations suggested for future research. ASBMR criteria are widely accepted, but have evolved and may be further refined in the future. We changed "standard" to "consensus" and cited the ASBMR criteria. Abaloparatide was added to the text. Details were added to the results and discussion sections on harms of long-term hormone therapy.
General	Public Commenter #7 (ASBMR)	Reasonable summary of the evidence.	Thank you for your comment.

Section	Commentator & Affiliation	Comment	Response
General	Public Commenter #7 (ASBMR)	It is unclear as to the rationale for setting the definition of "long-term" treatment at more than three years given that several of the larger, long-term studies looked at four and five years of treatment (e.g. FLEX and HORIZON Extension).	The context for this review was that broad consensus already exists about the efficacy of numerous drugs for reducing risk of fractures in patients with osteoporosis with treatment of up to 3 years. However, the clinical question was what is the evidence for benefits and risks beyond 3 years. We discussed whether trials like FLEX and the HORIZON extension should be categorized as long-term, drug holiday or both. To minimize redundancy, we only included studies that compared continuous osteoporosis drug treatment versus continuous placebo or other control in the section on long-term treatment. We placed studies of osteoporosis drug continuation versus discontinuation in the drug holiday section, regardless of the length of treatment before allocation to continuation or discontinuation and regardless of the duration of continuation. In the lead paragraphs of the different long-term results sections, we included a statement that treatment comparisons between continuation and discontinuation are located in a separate drug holiday section. We also added this explanation to the methods section to better orient readers navigating the report.
General	Public Commenter #7 (ASBMR)	It is important the report clearly explain that bisphosphonates and denosumab have uniquely different mechanisms of action on the offset of effect/rebound fractures.	In the introduction, along with text that notes the long-term persistence of bisphosphonates in bone, we added: "Drug holidays are not recommended after denosumab therapy because of post-hoc data indicating rapid bone loss after denosumab discontinuation and a possible slight post-treatment increase in risk of radiographic vertebral fractures." Further, we modified Table 1, inserting information on the mechanism of each osteoporosis drug therapy, including their different effects when discontinued.

Section	Commentator & Affiliation	Comment	Response
General	Public Commenter #7 (ASBMR)	Distinction between the strengths of evidence between the clinical trials and observational studies should be expanded. Report highlights the clinical trial evidence on the subject. While clinical trials are without a doubt the highest level of evidence, observational studies can be invaluable in uncovering rare but serious adverse events.	Most of the information in the draft report on harms, particularly on rare harms, was from observational studies. To make the source of the harms evidence clearer, in the report section detailing long-term treatment harms, we revised the key points to highlight what evidence came from RCTs and what came from observational studies.
General	Public Commenter #7 (ASBMR)	While post-hoc analyses are discussed, the effect of BMD achieved after initial therapy is not discussed (i.e. post hoc analysis shows that continued therapy is associated with a non-vertebral fracture reduction in patients with FN BMD less than -2.5).	We described the post-hoc findings the reviewer cites in the draft report at length: "A second post hoc FLEX analysis stratified further and reported that within the subset of women with a prevalent radiographic vertebral fracture at FLEX baseline, the effect of continued alendronate versus discontinuation on risk of incident nonvertebral fracture, clinical vertebral fracture and radiographic vertebral fracture did not differ as a function of baseline FN-BMD.(Schwartz JBMR 2010) In women without a prevalent radiographic vertebral fracture at FLEX baseline, the effect of continued alendronate versus discontinuation on risk of incident nonvertebral fracture differed as a function of baseline FN-BMD (interaction p-value 0.019). These results suggested that in women without a prevalent radiographic vertebral fracture at baseline, compared to women with higher baseline FN-BMD, women with the lowest FN-BMD levels may have greater reduction in risk of incident nonvertebral fracture with continued versus discontinued alendronate. However, the effect of continued versus discontinued alendronate on risk of incident clinical vertebral fracture or incident radiographic vertebral fracture did not appear to differ as a function of baseline FN-BMD (interactions not significant)." We highlighted these post hoc subgroup of a subgroup analysis findings in the key points at the top of the alendronate drug holiday effects section.
General	Public Commenter #7 (ASBMR)	Report should include the recent Ian Reid NEJM article study (DOI: 10.1056/NEJMoa1808082)	Thank you, this article was published after our draft report went out for public comment. It is included in the final report.

Section	Commentator & Affiliation	Comment	Response
General	Public Commenter #7 (ASBMR)	Should include recent pharmacoepidemiology data (Abrahamsen et al. DOI: https://doi.org/10.1136/bmj.i3365) around long-term bisphosphonates and fractures prevented/atypical fractures occurring. Such approaches are the only way to obtain adequate numbers of rare events such as AFF. Although these and other findings are not placebo controlled or RCTs, they do add to the interpretation of the evidence and they are ignored in the summary, abstract and discussion/conclusions.	We included pharmacoepidemiologic data in our review. However, we did not analyze data from the Abrahamsen article referenced by this reviewer because it was rated as having high risk of bias due to high detection bias and high attrition bias. With respect to detection bias, the S72.0x ICD-10 codes the authors used for potential AFF outcomes were very nonspecific and included all femoral head and neck fractures.
General	Public Commenter #7 (ASBMR)	Data are available of an increased risk of AFF and ONJ with longer term denosumab which isn't mentioned in the report.	Though outside the scope of this review, the strongest data on the association of denosumab with ONJ and AFF appear in patients with cancer receiving high doses. Though data from uncontrolled studies suggest a possible association between denosumab and risk of ONJ and AFF in patients treated for osteoporosis, too few patients have had ONJ or AFF in short-term denosumab RCTs to draw conclusions about an association and we identified no eligible long-term controlled studies in patients treated with denosumab for osteopenia or osteoporosis that reported information about risk of ONJ or AFF. This is an issue in need of future research, as we discussed in the revised discussion section.

Section	Commentator & Affiliation	Comment	Response
General	Public Commenter #7 (ASBMR)	It is now well accepted that stopping denosumab and not following with a bisphosphonate will cause rapid turnover and increased fracture risk - this should be mentioned in the document.	In the revised Introduction text, we added: "Drug holidays are not recommended after denosumab therapy because of post-hoc data indicating rapid bone loss after denosumab discontinuation and that suggest a possible slight post-treatment increase in risk of radiographic vertebral fractures." Further, we modified Table 1, inserting information on the mechanism of each osteoporosis drug therapy, including their different effects when discontinued. Additional information was added in the denosumab long-term harms and drug holiday results sections to address the lack of information from eligible studies on post-treatment vertebral fractures. Further, the lack of such data from eligible trials and the importance of further investigating this issue in future research were noted in the revised Discussion section.
General	Public Commenter #7 (ASBMR)	The tone of the document should emphasize the under treatment of osteoporosis, and a high priority for future research should be long-term treatment, with treatment free intervals, rather than simply a course of treatment.	The scope of this review as determined by AHRQ, NIH and the evidence team was not about whether current levels of treatment for osteoporosis are high enough. Including this information in the introduction would likely confuse readers about the purpose of the review. However, we addressed the issue of undertreatment in the future research recommendations part of the discussion. We also revised the future research needs section to recommend that future trials evaluate the effects of long-term osteoporosis drug treatment alternating with treatment free intervals.
General	Public Commenter #7 (ASBMR)	It is accepted that long-term bisphosphonates increase the risk of AFF. Document states "may" increase the risk. Should be changed to "are associated with an increased risk".	'May increase' was selected to best reflect the low strength of the evidence on risk of AFFs identified for this systematic review (i.e., long term trials and long term controlled observational studies).

Section	Commentator & Affiliation	Comment	Response
General	Public Commenter #5 (Karen Friday-International Society for Clinical Densitometry)	One of ISCD's major concerns is that the report lacks meaningful information concerning the use of dual-energy X-ray absorptiometry (DXA) to monitor bone density changes during long-term osteoporosis drug therapy. Increases in bone density during treatment are associated with reduction in fracture risk (benefits), and may be helpful in monitoring compliance with therapy. DXA may also be helpful in monitoring bone density changes during drug holidays or changes in therapy.	Per the protocol developed in consultation with AHRQ and NIH, the effect of early on-treatment change in BMD on risk of incident fracture was considered within the scope of the review, both during long-term treatment and during drug holidays. However, these early on-treatment changes in BMD were not themselves considered as an outcome. Per the protocol, we evaluated BMD change as an outcome only in long-term or drug holiday trials that also reported fracture outcomes. In these cases, we only looked at BMD changes as an outcome at the end of the follow-up periods. The use of BMD testing to monitor adherence with drug treatment was considered outside the scope of this review.
General	Public Commenter #5 (Karen Friday-International Society for Clinical Densitometry)	Regarding the potential mitigating effects of characteristics on risk of harms, recent reports have also shown that DXA may be useful in identifying incomplete atypical femur fractures (AFF). McKenna and colleagues demonstrated the use of single-energy femur scans at the time of DXA could detect subsequent radiographically-proven incomplete AFF in bisphosphate users with five years' exposure, and Van der Laarschot et al expanded the field with a larger cohort of femur scans, identifying incomplete AAF in 12 of 282 patients evaluated with DXA and treated with bisphosphonates or denosumab during the previous year. McKenna MJ, van der Kamp S, Heffernan E, Hurson C. J Clin Densitom. 2013 Oct-Dec;16(4):579-83.	Neither the McKenna nor van de Laarschot papers met eligibility for inclusion in our review, because they didn't include a control group and incomplete AFF was not an outcome of interest. However, they raise an interesting area for future research, whether risk of AFF is modified by DXA findings in patients receiving treatment with bisphosphonate or denosumab. We added this topic to our revised discussion section recommending future areas of research.

Section	Commentator & Affiliation	Comment	Response
General	Public Commenter #4 (Arthur Santora-Enter Bio, Ltd.)	"Limitations" on page ES-16 and "Limitations of the Evidence Base" on pages 85-86 are well written, but beg the question, "Are the data available sufficient to make reliable statements about long-term treatment beyond 4 years?" A similar question should be asked about adequacy of data to study the hypothetical risks (e.g., increased fracture risk) and hypothetical benefits (reduced risk of AFFs, ONJ and other potential adverse drug reactions) of discontinuing treatment with a bisphosphonate after 3 to 5 years (i.e., taking a "drug-holiday"). In "Strength of Evidence for Major Comparisons and Outcomes" on pages 13 and 14 the evidence of each outcome was to be rated "High," "Moderate," "Low," or "Insufficient." The strength of evidence rating system was generally followed when a statistically significant treatment effect was identified. However, there are numerous instances when 95% CI around the HR point estimate was so broad that nothing reliable can be stated about the treatment effect—yet the rating "insufficient" was not applied. There are several statements about the benefits and risks of continued treatment versus interruption of treatment after 3 to 5 years that state categorically that continued treatment does not lower risk of incident fractures. Careful evaluations of the data presented show that are too few fracture events to make any definitive statement about the effect of treatment and the rating "insufficient" data should have been reported.	Because the AHRQ definitions of low and insufficient SOE are at least partly subjective, it often is challenging to decide between low versus insufficient SOE grades when there is evidence that has multiple limitations. There is no consensus about what should tip the scale between no confidence and limited confidence in the estimate of the effect. SOE considered all domains, including consistency, and additional domains of strength of association, as well as the precision. Broadness of the confidence interval was assessed in relation to whether the "confidence interval was wide enough to include clinically distinct conclusions. In the text of the report, we tried to address any inconsistencies so as to not imply more certainty about low strength evidence.

Section	Commentator & Affiliation	Comment	Response
General	Public Commenter #6 (Jason Spangler & George Jarekso-Amgen)	The evidence on fracture risk for long-term DMB therapy versus placebo (Key Question 1) from the key eligible DMB study identified is not summarized consistently throughout the Draft Report.[2] In line with the Agency's conclusions in the Evidence Summary, Amgen does not consider this small phase 2 study to provide meaningful evidence on fracture risk for long-term DMB therapy, and a discussion of this study with our suggestion for revision is provided below. Evidence on fracture incidence, change in bone mineral density (BMD), and adverse events over up to 10 years of DMB treatment (relevant to Key Questions 1 and 3) is available from the much larger FREEDOM extension study.[3] Although this study was correctly excluded according to the systematic review inclusion criteria (due to its uncontrolled design), Amgen considers that it provides the most complete evidence to date on the efficacy and harm of long-term DMB treatment. Specific findings from this study are discussed below. [2]Miller PD, Bolognese MA, Lewiecki EM *et al.* Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone* 2008;43:222-229. [3]Bone HG, Wagman RB, Brandi ML *et al.* 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol* 2017;5:513-523.	In re-evaluating the evidence from this phase 2 denosumab trial on long-term fracture prevention for denosumab versus placebo, we agree with the reviewer that the statement of there being low strength evidence for no difference in risk of incident clinical fracture should be changed to there being insufficient evidence to draw conclusions about any differences between long-term denosumab and placebo. To ensure that we communicated about this finding consistently throughout the report, we added a bullet to the key messages at the start of the report stating: "No eligible trial provided usable data about whether long-term denosumab reduces risk of incident fractures." We modified Table A in the evidence summary to indicate that for long-term denosumab versus placebo, the evidence about the risk of incident clinical fractures is insufficient. The reviewer is correct that the FREEDOM extension study was not included in this review because the extension phase did not include a control group. By protocol, no studies without control groups were included in this review. The virtual placebo methodology remains susceptible to both selection and secular bias (Vittinghoff, Statistics in Medicine 2010;29:1127-36)..

Section	Commentator & Affiliation	Comment	Response
General	Public Commenter #6 (Jason Spangler & George Jarekso-Amgen)	Chapters 7 discusses the harms of drug holidays. While drug holidays may be an option for certain therapies, DMB should not be discontinued without considering transition to another antiresorptive agent due to the risk of multiple vertebral fractures.[1,4,5] Further information is provided below. [1]Amgen Inc. 2018. Prolia (denosumab) U.S. Prescribing Information, (06/2018). Cummings SR, Ferrari S, Eastell R *et al.* [4]Vertebral fractures after discontinuation of denosumab: A post hoc analysis of the randomized placebo-controlled FREEDOM Trial and its extension. *J Bone Miner Res* 2018;33:190-198. [5]Tsourdi E, Zillikens MC. Certainties and Uncertainties About Denosumab Discontinuation. *Calcif Tissue Int* 2018;103:1-4.	Thank you for your comment. In the report introduction, after the statement about the lack of consensus about bisphosphonate drug holidays (e.g., who should get them, when they should start and end, how they should be monitored, etc.), we added new language stating: "Drug holidays are not recommended after denosumab therapy because of post-hoc data indicating rapid bone loss after denosumab discontinuation and a possible slight post-treatment increase in risk of radiographic vertebral fractures.(Cummings JBMR 2018) In the report discussion, in part as suggested by Tsourdi and Zillikens (CTI 2018), we added the following recommendations for future research: (1) to better estimate the magnitude and duration of risk for post-denosumab vertebral fractures and fractures at other skeletal sites; (2) clarifying whether risk is due only to discontinuing an effective treatment or truly is increased compared to if patients had not received denosumab at all; and (3) evaluating the efficacy of different post-denosumab antiresorptive regimens for fracture prevention.
General	Public Commenter #6 (Jason Spangler & George Jarekso-Amgen)	Romosozumab is not yet FDA approved and therefore should be removed as an intervention. Given that there are no other treatments within the anti-sclerostin monoclonal antibody class, this treatment class should likewise be removed. Specific comments on these points are provided below.	Thank you for the comment. Romosozumab has been removed from the report as it was not FDA-approved at the time the public comment period ended.

Section	Commentator & Affiliation	Comment	Response
General	Public Commenter #7 (ASBMR)	The "key messages" about long-term bisphosphonate use do not address the fact that the benefit of longer-term use varies by fracture risk status. The findings of analyses like Schwartz et al, JBMR 2010, 25(5):976-82 (extended use of ALN reduced non-vertebral fractures in women with femoral neck T-scores -2.5 or worse after 5 years of ALN) are very important to our current evidence-based clinical practice. The AHRQ points either miss or deliberately ignore this kind of crucial nuance.	We did not believe these post hoc, subgroup of a subgroup findings warranted inclusion in the key messages at the head of the entire report. e Nevertheless, we neither missed nor deliberately ignored these findings. In the draft report, we described the Schwartz findings at length as follows: "A second post hoc FLEX analysis stratified further and reported that within the subset of women with a prevalent radiographic vertebral fracture at FLEX baseline, the effect of continued alendronate versus discontinuation on risk of incident nonvertebral fracture, clinical vertebral fracture and radiographic vertebral fracture did not differ as a function of baseline FN-BMD.(Schwartz JBMR 2010) In women without a prevalent radiographic vertebral fracture at FLEX baseline, the effect of continued alendronate versus discontinuation on risk of incident nonvertebral fracture differed as a function of baseline FN-BMD (interaction p-value 0.019). These results suggested that compared to women with higher baseline FN-BMD, women with the lowest FN-BMD levels may have greater reduction in risk of incident nonvertebral fracture with continued versus discontinued alendronate. However, the effect of continued versus discontinued alendronate on risk of incident clinical vertebral fracture or incident radiographic vertebral fracture did not appear to differ as a function of baseline FN-BMD (interactions not significant)." We also highlighted these findings in the key points at the top of the alendronate drug holiday effects section.
Front Matter	Public Commenter #7 (ASBMR)	The phrasing of many of the "key messages" is unnecessarily skeptical.	What is skeptical and what is unnecessarily skeptical is a subjective judgment. We sought to base our key message statements on the strength of the available evidence as we judged it using the methodology described in the report.
Abbreviations	Public Commenter #1 (Rafael Pirtillo Ferman -Altietus College)	Excellent use important for icd10 also	Thank you for the comment.

Source: https://effectivehealthcare.ahrq.gov/products/osteoporosis-fracture-prevention/research
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