Author's response to reviews

Title: The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women

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Version: 3 Date: 15 July 2011

Author's response to reviews: see over
Dear Editor of BMC Musculoskeletal Disorders

Thank you and your reviewers for providing comments to improve the paper. We found the comments very helpful. We have addressed each comment and provided a direct response to each suggested revision. Overall, we have provided greater clinical interpretation of the results including making a conclusion from the results, and we have provided clarifications for the analysis. We trust that you will agree that the revisions have contributed to an improved manuscript that is worthy of publishing.

Sincerely

Robert Borden Hopkins

Referee 1:

Reviewer's report
Title: The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women
Version: 2 Date: 3 June 2011
Reviewer: Iñaki Imaz
Reviewer's report:
This is a quite interesting article which tries to clarify an uncertain issue using new methods. Because its results don’t solve uncertainties, it is still more important to explain clearly the methods. This is the major weakness we must bring out.

Major compulsory revision:
1) The authors must report which are the baseline effects they establish to compare between prior to subsequent effects. The authors say that predefined priors were used but they don’t clearly explain how they reach those priors, or which information was used to calculate them.

Thank you for the clarifying comment. We have inserted into the methods a description of the effect of choosing weak priors. “Weak priors were chosen so that the final estimates for odds ratios are driven by the data, and not by any assumption made”.

In addition to this, the authors say
that (subsection of methods called “outcomes”) unadjusted odds ratios were estimated but they don’t say how they were calculated.

We have inserted in the methods a clarifying explanation. “For each outcome, the unadjusted odds ratio is derived from combining the odds ratio of each comparator versus a common group (i.e., Odds ratio of A/C = odds ratio (A/B) divided by odds ratio of C/B)”

2) The robustness assessment has not been clearly explained. First at all, the figures 2, 3, 4 and 5 should have title, and the results of differences between classical and Bayesian analysis should be clearly presented.

Titles to each of the columns in the forest plot are added and the caption indicates the description of each plot.

Minor essential revisions:
1) A minor but also compulsory revision of the abstract should be done because the results section says: “The drugs with the largest effect size for non-vertebral fractures was zoledronic or denosumab, while the drugs with the highest probability of reducing …” but it should be revised, saying: “were zoledronic and denosumab, while the drugs with the largest effect size for reducing …”

We have edited as suggested.

2) “Results” section. “Bayesian ITC estimate…” section. The first paragraph ends saying: “In addition, there is not enough evidence to detect differences in efficacy between any of the drugs” but it should be said: “… between any of the drugs for non-vertebral fractures”.

We have edited as suggested.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing
Referee 2:

**Reviewer's report**

**Title:** The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women  
**Version:** 2  
**Date:** 14 June 2011  
**Reviewer:** Lan Ho-Pham  

**Reviewer's report:**

Specific comments

However, having gone through the paper, I would like to raise a number of concerns which I hope the authors will take into account in their next submission:

1. The authors point out that a similar meta-analysis has been published, but they argue that there is a need for another meta-analysis. I think their argument is ok, because the present analysis offers indeed more information than the previous analysis. However, I think the authors could do more to bolster their argument. From a clinical point of view, I think we would like to know the clinically relevant effect rather than statistically significant effect (which the authors have done). In other words, could the authors define a region of clinical equivalence or non-inferiority and then work out the probability of clinically significant effect?

   *In the current version of the paper, we provide the highest probability of being the most efficacious versus placebo. We also provide the odds ratios versus placebo and the effect size versus placebo, and the odds ratio versus other drugs. We are reluctant to create a non-inferiority margin for a meta-analysis, without clear prior statement of what we think the margin should be. However, the probability of most efficacious creates a similar method for ranking the drugs. This is also relatively easier to interpret by a non-statistician.*

2. There are major differences in background risk among the trials which could potentially compromise the interpretation of comparison, and I am wondering whether one could directly compare treatment efficacy between trials?

   *While it is difficult to assess the impact that differences in baseline characteristics have on the odds ratio because of few trials for some drugs, a comparison of the difference in rate of fracture in the placebo arm of each comparator provides a quantitative measure of the effect of these differences. We have added to Table 2 the rate of fractures in the placebo arm for each comparator to allow qualification of the magnitude for the odds ratios. For most drugs the difference in baseline risk is not meaningfully different.*

3. Could the authors estimate the number needed to treat based on their indirect comparison?
Thank you the comment. We have added the NNT between each of the comparator drugs in Table 3. The ranking of the lowest NNT follows the ranking by probability of being most efficacious, but the NNT dose provide a clinical impact of the differences between drugs.

4. It seems that the authors are reluctant to make a specific conclusion (page 20). What is the “take home message” from this analysis? Is it reasonable to say that etidronate is the “best” drug in terms of non-vertebral fracture reduction?

We have added our interpretation of the drugs that are most efficacious. Although we are not confident to pick the best drug, three drugs (teriparatide, zoledronic code and denosumab) have favorable rankings across the different statistical measures. We have added this to the abstract.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests.

Reviewer 2: additional comments.

REPORT TEMPLATE
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Confidential comments to editors
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Please use this only for comments that relate to ethical or policy issues. Do not use it to repeat all or part of the comments in your review for the authors. These comments will not be included in the report passed to the authors or posted on the site.

Reviewer’s report
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General comments
This manuscript reports results of a meta-analysis of the relative efficacy of antiosteoporosis drugs currently in use for the prevention of fractures in postmenopausal women. In the absence of a head-to-head trial, I think this analysis is quite relevant. The analysis methodology (Bayesian modeling) is quite sophisticated, but it is perhaps best suited to this type of study.

- Minor Essential Revisions
The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

We have added more labels to graphs and checked for mistakes.
- Discretionary Revisions
These are recommendations for improvement which the author can choose to ignore. For example clarifications, data that would be useful but not essential. Please note that both the comments entered here and answers to the questions below constitute the report, bearing your name, that will be forwarded to the authors and published on the site if the article is accepted.

What next?

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Based on your assessment of the validity of the manuscript, what do you advise should be the next step?
- Accept after minor essential revisions (which the authors can be trusted to make)

Level of interest

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- An article whose findings are important to those with closely related research interests

Quality of written English

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- Acceptable

Statistical review

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- Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests

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I declare that I have no competing interests.
Reviewer's report

Title: The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women

Version: 2 Date: 15 June 2011
Reviewer: Patrick Haentjens

Reviewer's report:

Overall, the authors produced a methodologically quite robust paper incorporating all major references on this clinically relevant subject. Unfortunately, their statistical methods are so complex that many clinicians will be puzzled by whether the conclusions really make sense. A major concern in this regard already appears in the ABSTRACT where the Results section provides guidance for clinicians on the choice of osteoporosis medication followed by the Conclusion that significant differences between drugs in the odds of reducing fractures do not exist.

We have added our interpretation of the drugs that are most efficacious. Although we are not confident to pick the best drug, three drugs (teriparatide, zoledronic code and denosumab) have favorable rankings across the different statistical measures. We have added this to the abstract.

Equally important, use of indirect comparisons entails strong assumptions including, among others, comparability of event rates among control (placebo) participants. A clinician-oriented paragraph on this issue might be incorporated discussion.

Thank you the comment. We begin the discussion with a clinical interpretation of the results. In addition, we have checked the assumption of common placebo rates. The rate of fracture the placebo group for each drug is provided in Table 2.

Remaining issues

Page 15: Does an I² value of 64% really indicate moderate heterogeneity?

According to the most recent version of the Cochrane handbook, 64% now represents substantial heterogeneity and this has been revised in the text.

Page 15: What is the rationale for removing Cummings and Greenspan?

According to the Cochrane Handbook (reference 22) and previous work on ITC analysis, the ITC is more robust when heterogeneity is low. Top conduct ITC analysis, we then removed studies that contributed the most to heterogeneity.

Figures 3, 4, and 5: What are the events? Provide title for each Figure.
The number of events are provide in the forest plots. These figures have been revised to increase clarity.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests