Author’s response to reviews

Title: Adverse drug effects observed with Vildagliptin versus Pioglitazone or Rosiglitazone in the treatment of patients with Type 2 Diabetes Mellitus: A systematic review and meta-analysis of Randomized Controlled Trials

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POINT TO POINT RESPONSE TO REVIEWERS

Reviewer reports:

Hari Ananthula (Reviewer 1): Major Comments:

1. The background is too short. Please expand it to include any additional information relevant to this article. For example, mechanism of action of the drugs, approval status of the drugs in key regions and importance of this meta-analysis.

Author response: Thank you. Appropriate changes have been made as suggested. Hope the changes have improved the standard of the manuscript.

2. Page 8, Line 5 to 7: Elaborate why low publication bias was observed upon visual assessment of the funnel plot. I would suggest conducting a formal statistical test for detecting asymmetry in funnel plot, such as Egger's test or any such acceptable statistical test.

Author response: Because the number of studies were less, an Egger’s test would not be appropriate. However, the best way to show publication bias would be through funnel plots as we have shown in the manuscript. Asymmetry could easily be visualized. We have added some more description for clarity. Thank you.
3. In figures 2 to 6. Briefly indicate the interpretation of the forest plot somewhere in the results or link the forest plots to the results.

Author response: Thank you. Changes have been made as suggested.

Minor comments:

1) In the background section, rephrase the mechanism of action of vildagliptin, pioglitazone and rosiglitazone. Please indicate what class these compounds belong to.

Author response: Thank you. These suggested changes have been made.

2) Pg 4, Line 23-26: Is there any previous meta-analysis report in the literature comparing vildagliptin versus pioglitazone/rosiglitazone. If no such report exists, please rephrase the sentence by removing the sentence "meta-analyses have seldom been used". You may want to indicate that meta-analysis has not been performed before.

Author response: Yes. Thank you. Appropriate changes have been made as suggested.

3) Pg4, Line 34: Indicate in the text what databases have been searched

Author response: Thank you. We have indicated this information in the text.

4) Figure 1: Rephrase the sentence "records not related to our topic". Indicate what topic you are referring to.

Author response: Thank you. We have rephrased the sentence.

5) Results, Page 6, Line 23:"Five articles were further eliminated since they were case studies or meta-analyses". Do any of these five articles compare vildagliptin versus pioglitazone/rosiglitazone? If so, please add them in the reference and indicate how your article is different from their article.

Author response: No, they were not directly related to the exact comparison. And since they are not among our eligible criteria, these studies were excluded (not relevant to the study).
6) Pg 7, line 12: Rephrase the statement "Dizziness significantly favored pioglitazone/rosiglitazone"

Author response: Thank you. This statement has been rephrased.

7) Pg 7, Line 19: After the following text, please indicate the p value criterion used for assessing the statistical significance. "the results were not statistically significant (Figure 2)"

Author response: Thank you. The corresponding P values were indicated in the same sentence.

8) Page 8, Line 49: "This study is new in the way that it is among the first meta-analyses comparing adverse drug events between vildagliptin and pioglitazone or rosiglitazone in patients who were treated for T2DM." Is this study the first meta-analysis comparing AEs between vildagliptin and pioglitazone or rosiglitazone. If so, please rephrase this sentence and indicate that it is the first such study.

Author response: Thank you. Appropriate changes have been made.

9) In table 2, under the column "drug used in experimental group", add Vildagliptin since this drug is used as well.

Author response: Thank you. Appropriate changes have been made.

10) In Table 2, As per Bolli2008 article, total number of patients treated with Pioglitazone or Rosiglitazone are 281 and not 280. Please double check this number in the article.

Author response: Dear reviewer, I agree that the total number of patients was 281. However, when it comes to outcomes, 280 patients were assessed for outcomes (see table 3 of study Bolli2008). Thank you.

11) Page 9, Line 20: Conclusions: "However, peripheral edema and weight gain were significantly higher with rosiglitazone. Further studies need to confirm these hypotheses."

a. Indicate what kind of further studies are needed to confirm this observation?
Author response: Further studies include future randomized controlled trials. Therefore, we have clarify in the conclusion, what were these further studies. Thank you.

Alfred Balch (Reviewer 2):

The overall conclusion, that there is not a difference in overall risk for vildagliptin vs. rosiglitazon/pioglitazone, except that dizziness is reduced for the rosiglitazone/pioglitazone group seems well supported by the data, with the OR CI .81-1.24 within acceptable bounds. The other findings seem to either be post-hoc (comparisons to rosiglitazone only) or not supported by statistically significantly different results (e.g. weight gain). Results which are post-hoc must be separated and distinguished, and no claim of difference can be made for non-statistically significant difference in Odd Ratio. I have attached a Word documents with comments.

Author response: Thank you. We have tried to correct the conclusion accordingly. Concerning weight gain and peripheral edema, further studies will be able to confirm their status, that is, in future studies. Thank you very much.