Author’s response to reviews

Title: Glucagon like Peptide Analogues for Type 2 Diabetes Mellitus: Systematic Review and Meta-analysis

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Author’s response to reviews: see over
Dear Editors,

Please find attached a revised version of our paper, with changes in response to the second set of comments from Olivia Phung. Her comments and our responses are tabulated below.

<table>
<thead>
<tr>
<th>Comment</th>
<th>Response</th>
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<tbody>
<tr>
<td>The thresholds for the interpretation of $I^2$ are not mutually exclusive and there is considerable overlap between categories. Please clarify how an analysis falling in two categories would be assigned.</td>
<td>We referred to the distribution recommended in the Cochrane Handbook. However in practice we explored reasons only for heterogeneity above 70% (which we called “substantial”), and were interested mainly in differences in direction of effect, rather than effect size. The $I^2$ test is a bit over-sensitive (see for example figure 7, third plot, where $I^2$ is 81% but the actual differences are not clinically significant). We have deleted the statement and replaced it with a reference to levels between 70% and 84% being substantial, and 85 and over as being highly significant, reflecting the terminology used in the results.</td>
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<td>I am unclear how the authors arrived at mean age, baseline A1c, etc for their study characteristics. Did the authors meta-analyze this baseline data in Review Manager and report it here? Reporting the mean number of participants in each trial seems flawed; it can only be calculated from a simple average and may not be representative of the data. Why not a median?</td>
<td>The means are averages across trials, i.e. the means of the means. This is quick and we thought reasonable. However we have changed this sentence to read: “The mean ages of patients in the trials ranged from 52.6 to 60 years; mean baseline HbA1c ranged from 7.3% to 10.2% and mean BMI from 25 to 35.” None of the trial reported medians so it was not possible to use medians.</td>
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<td>The rationale given for excluding Rosenstock 2009 from the analysis on the basis of metformin is inadequate. Needs</td>
<td>The exclusion was because all patients in the exenatide arm were on metformin, whereas only some of those in the albiglutide arm</td>
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some elaboration on why inconsistent metformin use would affect study results. Also, there needs to be a statement of whether this was an a priori exclusion criteria in the Methods section or a post-hoc decision. Otherwise, it appears that this study was singled out.

In both the Results and Discussion sections: The author responses state that weight loss being independent of nausea was a stated result of a study and no numerical data were available. If this is the case, please cite accordingly and qualify statements that no numerical data were available. Otherwise, this claim is unsupported as it stands in the manuscript.

Discussion: Authors state that exenatide 10 mcg bid was equivalent to insulin and rosiglitazone. The author's response to the comment adequately addressed my concern, but no clarifications to the manuscript were made. The authors appear to base equivalence on a clinically relevant A1c threshold of 0.5%. This information should be added to the Discussion section with a reference to a source that supports that threshold.

The authors state that the incidence of hypoglycaemia was low with GLP-1 agonists, but did mention what the comparison was to judge low. The response to comment states that this is low in absolute terms. This then needs to be qualified in the manuscript, by stating that the absolute incidence is low. Otherwise, “low” itself is a relative term.

Prepared by:

Deepson Shyangdan, research assistant and Norman Waugh, professor of public health and head, Aberdeen Health Technology Assessment Group.