Reviewer's report

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

Version: 1 Date: 9 September 2010

Reviewer: Olivia J Phung

Reviewer's report:

Major Compulsory Revisions

General Comments
1. Much text is spent on mentioning individual study sponsors for each endpoint/analysis. Single mention in study characteristics section and as a limitation in the discussion may be sufficient. The authors appear to be very suspicious of industry-funding and it is distracting from the results of the meta-analysis.

Methods
2. The acknowledgements section leads the reader to believe that authors were contacted for additional data. Please add this into the methods section and then report in the results which studies provided additional data.
3. Provide acceptable (clinically relevant) GLP-1 analog doses for inclusion into your review.
4. The validity assessment section does not present a scoring system for determining high or moderate quality evidence, but the Results section refers to “high quality” trials. Please clarify.
5. Page 7, Line “Ideally, studies would have provided data on cardiovascular events and other complications, but all were too short in duration.” This line is an editorial comment which may be more appropriate in the discussion of limitations.
6. Quantitative data synthesis:
a. Clarify how the studies will be pooled, knowing that there are different GLP-1 analogs and active comparators.
i. For GLP-1 analog versus placebo, it appears that different doses and individual agents were pooled together. Why was this not done for GLP-1 analogues versus active comparators?
b. Clarify which endpoints will be pooled with meta-analysis and which endpoints will only be summarized qualitatively.
i. Provide rationale for selecting specific endpoints to pool.
c. Specify which type of data is required for pooling categorical and continuous data. (event rates, changes from baseline and standard deviations, etc)
d. Provide interpretation of I2 statistic.
Results

7. The total analysis of GLP-1 analogs versus placebo is methodologically flawed. There do not appear to be any adjustments for including multiple arms of the same study. No adjustments are mentioned in the Methods section, and looking at Figure 2, there are no apparent adjustments when totaling the number of patients in both groups. Please refer to the Cochrane Handbook (Chapter 16.5.4 How to include multiple groups from one study) on how to properly account for the patients in the placebo group multiple times. Without proper methods here, the results are skewed since the patients in the placebo groups of Kaku 2010, LEAD 1, LEAD 2, and LEAD 4 are double or triple counted in the overall analysis.

8. Liraglutide 0.6 mg/day is an initiation dose for one week, not a clinically relevant maintenance dose. Liraglutide should be titrated to a maintenance dose of 1.2 mg/day. Pooling data with liraglutide 0.6 mg/day and 0.9 mg/day may not be clinically relevant.

9. Figure 1: Details for exclusion should be provided for every step. Please clarify how 170 full text articles were assessed, but only 51 RCTs were retained for further analysis. Typically full-text detailed evaluation occurs in a single step. Please refer to the PRISMA statement for the formatting of this figure.

10. Study characteristics: The mean age, baseline A1c, and number of participants is provided. How were these means obtained? This does not appear to be an individual patient data meta-analysis. It would be more appropriate to report the median and range, since the only data you have is the mean from each individual trial.

11. How did the imbalances in concomitant medication affect your analysis? This paragraph may fit better as a limitation in the discussion section.

12. Page 9, Line “In Rosenstock 2009, a group receiving exenatide was excluded, as all participants in this group also received metformin, whereas only a proportion of the patients in the other groups did.” This does not appear to be an a priori exclusion criteria. What is the rationale for excluding this arm?

13. Study quality: The definition of moderate to high needs to be explained in the methods section.

14. Page 10: Derosa 2010 was excluded from the analysis of GLP-1 analog versus active comparators for insufficient details. What type of details were missing? Like with the other excluded studies for GLP-1 analog versus placebo, could have provided the qualitative results from that individual study.

15. HbA1c: For the comparison of GLP-1 analog with active comparators, the results of individual trials are reported as changes from baseline and not mean differences that the methods state as the preferred expression for continuous variables.

16. Achieving HbA1c <7%: For the comparison of GLP-1 analog versus active comparators, the methods state that this would be expressed as relative risk, however the results text simply provides percentages and p-values.
17. Page 14, Line “Weight loss occurred in patients not experiencing nausea.” Justify this statement with data.

18. Body weight should be reported as mean differences per your pre-specified methods.

19. It does not appear that FPG and PPG were meta-analyzed, but an I2=0% was reported for FPG of exenatide 10 mcg vs glargine. Please clarify. If FPG and PPG was indeed meta-analyzed, provide results. If not, provide rationale for why not.

20. It is unclear why the results of blood pressure and lipids are included. Was there a pre-specified rationale for GLP-1 analogues’ effect on these parameters? Also, provide reference to table for numerical results.

21. Lipid profile: Results presented look like changes from baseline and not comparisons between the GLP-1 analogue and its active comparator.

22. Beta-cell function: Refer to table and/or provide numerical data.

23. For all endpoints, there should be parallel writing. For A1c, A1c goal, and weight the results appear to be presented as GLP-1 versus placebo, then GLP-1 versus active control. This pattern does not continue through the rest of the endpoints, making results text difficult to read.

24. QOL: Again, should focus on reporting the differences between groups, rather than reporting the changes for each group from baseline.

25. Hypoglycemia: Why was this endpoint not meta-analyzed?

26. Be consistent with the study descriptions of GLP-1 analogues in combination with baseline therapy. For hypoglycemia there is report of combinations with sulfonylureas affecting the endpoint, but combinations were not mentioned for the other endpoints. If sulfonylurea use affected the outcome, this may fit better in the discussion section.

Discussion

27. Summary of principal findings is based on comparison with active comparators, but the main analysis was versus placebo.

28. Page 21, Line “…can be an alternative to immediate insulin in patients failing on combined oral glucose lowering agents.” Statement may not be justified since only a few trials were directly compared to insulin.

29. Page 21, Line “exenatide 10 mcg twice daily was equivalent to both insulin and rosiglitazone…” I do not believe that the analysis was sufficiently powered for equivalence. This likely suffers from type 2 error, where there was no statistically significant differences, but may be premature to declare equivalence.

30. Page 21, Line “Weight loss was independent of nausea.” There was no analysis done to support this statement.

31. Page 22, Line “We did not include any unpublished data.” This statement is somewhat untrue since the acknowledgements section leads me to believe that you contacted authors for unpublished data or clarification. Also, this is a major limitation which could lead to skew of final results due to publication. There was
also no analysis for publication bias.

32. Page 23, Be wary in making indirect comparisons between liraglutide and once weekly exenatide. This is a weak argument.

33. Page 24, Line “There is only one trial of GLP-1 agonists against pioglitazone…” This statement does not relate to the paragraph about comparison to insulin.

34. It is stated that only two trials lasted 52 weeks. Were clinical trial registries checked to see if published trials were still ongoing?

35. Discussion of beta cell function needs better link to the current review.

36. GLP-1 analogues’ role in clinical practice not clearly described in discussion. Not sure if the author is promoting its use in dual therapy or triple therapy.

37. Ongoing trials: provide references to the clinicaltrials.gov entry or methods papers.

Minor Essential Revisions

General Comments

38. Grammar could be improved throughout the manuscript.

39. Appropriate references need to be added throughout the text. In-text citations are still necessary even when referring to studies by author and year.

40. Avoid using nonstandard abbreviations in text and tables (BiAsp, Exe, Lir, etc).

41. GLP-1 is not the proper name for this class of drug; should be GLP-1 analog or agonist throughout text. Be consistent with which term is used.

Abstract

42. Please add an objective or hypothesis statement to the background.

43. Please add databases searched.

44. The median length of trials may go into the results section, rather than the methods.

Background

45. The section on currently available and recommended treatments for type 2 diabetes could be shortened.

Methods

46. The inclusion and exclusion criteria for trials may fit better in the selection section. It makes more sense to know what studies were eligible before describing the validity assessment and data abstraction.

47. The primary and other outcome measures may better fit into the data abstraction section, rather than the study characteristics section.

Results

48. Trial flow: Provide information about the initial records found through the search.
49. Report of minor hypoglycemia should start a new paragraph.
50. Page 19, Line “The incidence of major hypoglycemia was low with GLP-Is.”
   Compared with what?
51. Much of the hypoglycemia data is already presented in Tables.
   Figures and Tables
52. All figures need legends with abbreviations.
53. Figures 3, 5, and 7 very difficult to read. Text is stretched out.
54. Table 4 requires legend with abbreviations.

Level of interest: An article whose findings are important to those with closely
related research interests

Quality of written English: Needs some language corrections before being
published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.