Author’s response to reviews

Title: Prokinetics for the Treatment of Functional Dyspepsia: Bayesian Network Meta-analysis

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Prokinetics for the Treatment of Functional Dyspepsia: Bayesian Network Meta-analysis

Dear Editors and Reviewers

First of all, authors appreciate the editors’ and reviewers’ thoughtful and helpful comments. Also, we are pleased to have an opportunity to make this paper to be an even better one and to be accepted with major revision, because the editors and reviewers provided additional important points that we haven’t realized before.

Here, we are submitting the revised manuscript that addresses several concerns of the editors and reviewers. We have included the changes as recommended by the editors and reviewers in the revised manuscript (colored as red).

We hope that this paper will now be considered for publication.
We thank you for your time and look forward to your reply.

Sincerely yours,

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Point-to-point responses

Reviewer 2


First, the authors wish to thank to the reviewer for offering careful and helpful comments.

R1. There have been 2 meta-analyses by Hiyama et al. (J Gastroenterol Hepatol. 2007 Oct;22(10):1566-70. Treatment of functional dyspepsia with serotonin agonists: a meta-analysis of randomized controlled trials / J Gastroenterol Hepatol. 2007 Mar;22(3):304-10. Meta-analysis of the effects of prokinetic agents in patients with functional dyspepsia.), which addressed total efficacy of prokinetics or serotonin agonists for the treatment of functional dyspepsia. These studies cannot present the comparative efficacy, which agent has better therapeutic ability than the others. They only can provide prokinetics or serotonin agonists are effective or not in the treatment of functional dyspepsia. Therefore, we aimed to present the network meta-analysis and
these contents were added in the Background section as colored red. Thanks again for giving us a thoughtful comment.

2. -page 3 line 13, when first used "ORs", please spell up in full eg., odd ratio (OR)

We appreciate the reviewer’s thoughtful comment.

R2. The ORs in the abstract section was corrected as ‘odds ratios (ORs)’ according to the reviewer’s suggestion (colored red). Thanks again for giving us an helpful comment.

3. -please state the reason why Bayesian meta-analysis was used in this study and not the classical meta-analysis you can run in RevMan was used?

We appreciate the reviewer’s helpful comment.

R3. We think R1 question has the similar point for correction with R3 question. We added different point in terms of the aim of this study compared to previous published meta-analysis (comparative efficacy in each prokinetic agents in Network meta-analysis vs. total pooled efficacy of prokinetic agents in previous classical pairwise meta-analysis) in the Background section (colored red). Thanks again for your thoughtful comment.

4. -Table 2, please be consistent with the decimal used.

We appreciate the reviewer’s thoughtful comment.

R4. The decimal was corrected as the reviewer’s suggestion in the Table 2 (colored red). Thanks to reviewer again for important comment.

5. -Table 3, please indicate what are the value within the table? OR? 95%CI?

Authors wish to thank to the reviewer for offering careful and helpful comments.

R5. Legend were added in the Table 3 as “Odds ratio with 95% credible interval is described in each column. Prokinetic agent in the top left means better efficacy and statistical validity is
guaranteed when the 95% credible interval does not include 1.” Thank you again for giving us an important comment.

6. -can you assess heterogeneity of your included studies?

Authors wish to thank to the reviewer for offering careful and helpful comments.

R6. Classical pairwise meta-analysis rigorously investigates the reason of heterogeneity using meta-regression, subgroup analysis, and sensitivity analysis. However, network meta-analysis includes multiple heterogenous treatment arms and the aim of this analysis is comparing relative efficacy of each treatment. Therefore, this has inherent limitation that cannot find the exact reason of heterogeneity unlike pairwise meta-analysis. And this content is described in the discussion section as “In this study, we could not investigate the reason for the relatively lower efficacy of itopride, a mixed D2 receptor antagonist, and acetylcholinesterase inhibitor or acotiamide, an M1/M2 muscarinic receptor antagonist and acetylcholinesterase inhibitor. Given the probability of inconsistencies in the enrolled studies and the superior efficacy of prokinetics that have a relatively small number of enrolled population, there could be an overestimation of efficacy drawn from the pairwise indirect comparison.” Thanks again for thoughtful comment.

7. --Data extraction form used in this study should be attached as appendix or supplement.

Authors wish to thank to the reviewer for offering careful and helpful comments.

R7. Data input excel file was added in the ‘Additional files’ section as a name of appendix.xlsx

Thanks again for giving us an important comment.
Reviewer 3

1. Abstract:

- Use the abbreviation of FD
- Full description of RCT is missing
- Include p-values to state significance

Authors wish to thank the reviewer for offering careful and helpful comments.

R1. The abbreviation of FD is described in the 1st sentence of abstract. Full description of RCT was added in the abstract (colored red). P values are not described in the network meta-analysis because ranking of multiple comparison is the primary outcome of network meta-analysis. Statistical validity is guaranteed when the 95% credible interval does not include 1. And this content was added in the manuscript (last sentence in the methodology section). Thanks again for your helpful comment.

2. Background:

- Background description is too short

Authors wish to thank the reviewer for offering careful and helpful comments.

R2. The Background section was modified according to the reviewer’s suggestion. The definition of FD and description of subtypes were added (colored red). Thanks to reviewer again for thoughtful comment.

3. The authors claim that FD occurs in 30-40% of the population, while in the paper they refer to the prevalence is much lower, please explain

Authors wish to thank the reviewer for offering careful and helpful comments.

R3. Although El-Serag HB et al. [1] reported pooled prevalence of FD as 11.5-14.7%. The heterogeneity of each studies in the systematic review made it difficult to calculate the total prevalence of FD (only 2 studies were used calculating pooled prevalence of FD). In that paper (citation number 1), figure 2 describes the wide range of prevalence of FD according to the definition and geographical difference. We cited this content but there could be a
misunderstanding. To reduce the misunderstanding of exact prevalence of FD, we corrected sentence as “Functional dyspepsia (FD) is a common condition in clinical practice [1]”. Thank you again for giving us an important comment.

4. - Symptom description according to Rome III is missing, also a general description of FD should be included together with the two subtypes of FD

R4. The Background section was modified according to the reviewer’s suggestion. The definition of FD and symptom description of subtypes were added (colored red). Thanks to reviewer again for helpful comment.

5. - An introduction of the different prokinetics is missing

R5. We could not add the detailed pharmacological classification of prokinetics in the Background section. However, these sentences were added to ensure the aim of this study which is the evaluation of the comparative efficacy of different prokinetics; “Moreover, previous published pairwise meta-analyses analyzing of drugs with different mechanisms as a single prokinetic agents or serotonin agonists presented total efficacy of prokinetic agents, but cannot distinguish the response of each drug which has different action mechanism [8, 9].” The detailed pharmacological explanation of each prokinetic agent is described in the discussion section. Thanks to reviewer again for thoughtful comment.

6. - If there was no language restriction, how where the papers in Chinese and Portugues interpreted

Authors wish to thank to the reviewer for offering careful and helpful comments.

R6. Many meta-analysis exclude non-English papers although these are found in the core databases. We found some non-English papers in core databases and translated these into English language using commercial translation service.

7. How was significance determined for the ORs?
Authors wish to thank to the reviewer for offering careful and helpful comments.

R7. Network meta-analysis using Markov chain Monte Carlo method does not present the p-value. If credible interval contains 1, the OR does not have statistical significance. Therefore, we used terms such as “not significantly different.” in the manuscript if credible interval contains 1. And this explanation was added in the last sentence of methodology section. Thanks to reviewer again for thoughtful comment.

8. Reference 36 in the text on line 190 has the wrong configuration

Authors wish to thank to the reviewer for offering careful and helpful comments.

R8. The reference was corrected as the reviewer’s suggestion. Thanks again for your helpful comment.

9. p-values of the ORs are missing

Authors wish to thank to the reviewer for offering careful and helpful comments.

R9. Network meta-analysis using Markov chain Monte Carlo method does not present the p-value. If credible interval contains 1, the OR does not have statistical significance. Therefore, we used terms such as “not significantly different.” in the manuscript if credible interval contains 1. And this explanation was added in the last sentence of methodology section. Thanks to reviewer again for thoughtful comment.

10. Values of fig 3 and table 3 are different, though they represent the same data

Authors wish to thank to the reviewer for offering careful and helpful comments.

R10. There were typographical errors in the process of presenting decimal and WinBUGS setting errors (Burn in Runs). All the outcomes were corrected on the basis of forest plot (fig 3). Thanks again for reviewer for giving us an important comment.
11. I have the feeling that there is a lot of overlap between the figures and the tables. The authors should decide with figures or tables would best represent the data and eliminate recurring data.

Authors wish to thank to the reviewer for offering careful and helpful comments.

R11. Because rankogram does not present the additional information for readers, we removed figure 4 according to the reviewer’s suggestion. Although other figures and tables have similar meaning (ex, SUCRA value and league table..), the statistical method for presenting comparative efficacy is different. Therefore, we decided to remove only figure 4. Thanks to reviewer again for thoughtful comment.

12. Figures:  - The resolution is too low  - Legends need to contain more information

Authors wish to thank to the reviewer for offering careful and helpful comments.

R12. The resolution of figures were modified and legends were added. Thanks to reviewer again for thoughtful comment.

13. Table 1:
- Also include the gender and age distribution for each study

Authors wish to thank to the reviewer for offering careful and helpful comments.

R13. The table 1 was modified according to the reviewer’s suggestion. Thanks to reviewer again for helpful comment.

14. What were the adverse events per study if present and the dosages/administration route of the prokinetics (Table 1).
Authors wish to thank to the reviewer for offering important comments.

R14. Adverse events related to prokinetics were summarized and added in the result section (colored red). All the drugs were orally administered and this content was added in the result section (page 9). The detailed dosage and duration of prokinetics were added in the Table 1. Thanks to reviewer again for helpful comment.

15. What is meant by the effective vs total, please explain as no further explanation is given in the text (Table 1).

Authors wish to thank to the reviewer for offering careful comments.

R15. Legend was added for better understanding of readers as “Effective/Total means number of symptom improved patients/total number of patients for given each prokinetic agent.” (colored red). Thanks to reviewer again for helpful comment.

16. It has been described that FD patients have impaired accommodation. Could it be that the lack of symptomatic relief after prokinetics could be due to a negative effect on gastric accommodation?

Authors wish to thank to the reviewer for offering careful comments.

R16. Impaired gastric accommodation is suspected as one of the pathophysologic mechanism of FD. Itopride, acotiamide, buspirone, motilitone (DA-9701), and mosapride are known agents for the enhancement of gastric accommodation. In this study, mosapride showed relative higher efficacy than those of itopride or acotiamide. Meta-analysis cannot present exact reason of the statistical different efficacy of these agents. As prescribed in the 1st paragraph of discussion section, multiple pathophysiological mechanisms are suspected for the symptoms of FD. Therefore, this sentence was added in the discussion section as “For example, although mosapride, itopride, and acotiamide are all known to modulate gastric accommodation, the statistical effects of these drugs differed in this analysis [46-48].”. Thanks again for reviewer for giving us an important question.

Authors appreciate the editors’ and reviewers’ thoughtful and helpful comments again.