

Title: Efficacy and Safety of Non-pharmacological Interventions for Irritable Bowel Syndrome in Adults. (Manuscript NO.: 58077)

Dear Editors and Reviewers:

Thanks for your letter and for reviewer comments concerning our manuscript entitled “Efficacy and Safety of Non-pharmacological Interventions for Irritable Bowel Syndrome in Adults”. (Manuscript NO.: 58077). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to editors and reviewers comments are as follows:

Responds to editors and reviewers comments:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This paper is a comparative study of pharmacological, non-pharmacological, and acupuncture treatments of IBS. Few papers on this topic are present. It is believed that this paper will assist readers in selecting treatment options for IBS.

Response: Thanks for your nice comments. Indeed, the aim of our manuscript is to compare non-pharmacological interventions including biofeedback, cognitive behavioural therapy, probiotics, dietary, acupuncture and moxibustion in the treatment of IBS. We also hope that this paper will be to some extent recommended several interventions for clinical practice and assist readers in selecting treatment options for IBS. As for Scientific and Language Qualities, we tried our best to improve the manuscript and made some changes accordingly in the manuscript. These changes will not influence the content and framework of the paper. Should there been any other corrections we could make, please feel free to contact us.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The manuscript entitled "Efficacy and Safety of Non-pharmacological Interventions for Irritable Bowel Syndrome in Adults" in the form of a literature review addresses a topic widely used in the clinical practice and therapy of patients with IBS. However, studies comparing pharmacological and non-pharmacological intervention in patients with IBS are scarce in the literature. The present study is an excellent contribution to the therapeutic topic of IBS, and provides a stimulus for conducting comparative studies of these therapeutic options.

Response: Thanks for your appreciation and warm work earnestly. We also hope that our manuscript may supplement the recommendations of existing guidelines and guide clinical practice in the treatment of IBS. As for Scientific and Language Qualities, we tried our best to improve the manuscript and made some changes accordingly in the manuscript. These changes will not influence the content and framework of the paper. Should there been any other corrections we could make, please feel free to contact us.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: it is an interesting review. The authors should include some information regarding the IBS genetics and how genetics may influence the innervations. The authors should include relevant reviews ie Nat Rev Gastroenterol Hepatol. 2016 Feb;13(2):77-87

Response: We would like to express our great appreciation to you on this paper. These comments are all valuable and very helpful for revising and improving our manuscript, as well as the important guiding significance to our researches. According to your comments, the statement "With the exception of the potential factors mentioned earlier, genetic findings about IBS

pathogenesis should also be taken into consideration. Gazouli *et al*^[72] have confirmed that single nucleotide polymorphisms in genes of serotonergic signalling pathway are associated with at least a subgroup of IBS. For instance, patients who carry an S allele or S/S genotype have differences in the central processing of visceral pain, which could result in a high susceptibility to negative emotional memory and contribute to enhance visceral pain perception^[73-74].” was added on our revised manuscript (p. 9, lines 1-6).

Editorial Office’s comments:

(1) Science Editor:

1 Scientific quality: The manuscript describes a meta-analysis of the non-pharmacological interventions for irritable bowel syndrome. The topic is within the scope of the WJG. (1) Classification: Grade B, Grade B and Grade C; (2) Summary of the Peer-Review Report: This paper is a comparative study of pharmacological, non-pharmacological, and acupuncture treatments of IBS. Few papers on this topic are present. It is believed that this paper will assist readers in selecting treatment options for IBS. The authors should include some information regarding the IBS genetics and how genetics may influence the innervations. The questions raised by the reviewers should be answered; and (3) Format: There are 5 tables and 10 figures. A total of 85 references are cited, including 19 references published in the last 3 years. There are no self-citations.

Response: Thanks for your summary. We have done accordingly based on the Peer-Review Report: the statement “With the exception of the potential factors mentioned earlier, genetic findings about IBS pathogenesis should also be taken into consideration. Gazouli *et al*^[72] have confirmed that single nucleotide polymorphisms in genes of serotonergic signalling pathway are associated with at least a subgroup of IBS. For instance, patients who carry an S allele or S/S genotype have differences in the central processing of visceral pain, which could result in a high susceptibility to negative emotional memory and contribute to enhance visceral pain perception^[73-74].” was added on our revised manuscript (p. 9, lines 1-6).

2 Language evaluation: Classification: Grade B, Grade B and Grade B. A language editing certificate issued by EnPapers was provided.

Response: Thanks for your consideration.

3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Copyright License Agreement, and the PRISMA checklist form. The authors need to complete the Conflict-of-Interest Disclosure Form. No academic misconduct was found in the Bing search. The highest single-source similarity index in the CrossCheck report showed to be 7%. Please rephrase these repeated sentences.

Response: Thanks for your reminding. Based on your suggestions, we have completed the Conflict-of-Interest Disclosure Form. Meanwhile, we also have rephrased these repeated sentences on our revised manuscript: “Data of included publications were analyzed using network meta-analysis (NMA). Quality of endpoints were assessed by tools of the Cochrane Handbook and the GRADEpro software” (p. 2, lines 6-8); “Then, 10 thinning intervals each Markov chain and 50 thousand iterations were equipped so as to obtain their posterior distributions” (p.5, line 30 to p. 6, line 1); “**Study Selection:** All of the 1592 literatures were identified from five data libraries based on the well-established retrieval.” (p. 6, lines 9-11); “(i) Selection bias: 30 trials grouped patients according to detailed randomized algorithms while the rest 10 only described “randomization”.” (p. 6, lines 16-17); “**Quality Esitmates Based on the GRADE System:** For the primary endpoint, Figure 10 showed that the quality of esimates was “Low”. Considering the information about GRADE criteria, the result was possibly derived from quality ratings of direct and indirect comparisons within RCTs, thereby leading to imprecision and unclear risk of bias.” (p. 8, lines 12-16); “Results showed comprehensive analysis of data for retrievable IBS interventions at present.” (p. 8, lines 21-22); “Consistency is viewed as an one-way comparative relationship between direct and indirect evidences in an NMA” (p. 9, lines 19-20); “clinical heterogeneity such as the improvement of IBS-SSS, SAS and SDS which were evaluated by an excessive personal opinion from professional practioners or participants should be noticed.” (p. 9, lines 22-24); “the methodological quality of all RCTs was moderate and quality esitmates based on the GRADE system showed “Low”” (p. 9, lines 29-30).

4 Supplementary comments: This is an unsolicited manuscript. The study was performed with 5 financial supports. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG.

Response: Thanks for your positive comments. Indeed, our manuscript is an unsolicited one. Our study was performed with 5 financial supports and the topic has not previously been published in the WJG. I have not published articles in the BPG.

5 Issues raised: (1) I found no “Author contribution” section. Please provide the author contributions; (2) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (3) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (4) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

Response: Thanks for your valuable suggestions to improve the quality of our manuscript. Based on your comments, (1) we have provided the author contributions: “**Author Contributions** Conceived and designed the Study: Ling Hu, Liming Lu. Performed the experiment: Yun-kai Dai, Yun-bo Wu. Analyzed the data: Yun-kai Dai, Yun-bo Wu. Wrote the paper: Yun-kai Dai. Study supervision: Ru-liu Li, Wei-jing Chen, Chunzhi Tang, Liming Lu, Ling Hu. All authors approved the final manuscript as submitted.” (p. 11, lines 16-20). (2) We have uploaded the funding agency copy of these approval documents, attached please find the revised version. (3) We have prepared and arranged the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor, attached please find the revised version. (4) We have provided the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references on our revised manuscript. However, because these literatures including graduation theses are retrieved by the Chinese database of CNKI, references No. 30-31, 33-37, 39-42, 44, 46-47, 51, 53-56, 59-60, 64, 66, 68-69, 71 have only DOI citation numbers and references No. 32, 38, 45, 49, 57, 63, 67 have no PubMed numbers or DOI citation numbers.

6 Re-Review: Required.

Response: Thanks for giving us an opportunity to revise our manuscript.

7 Recommendation: Conditionally accepted.

Response: Thanks for your appreciation.

(2) Editorial Office Director: I have checked the comments written by the science editor.

Response: Thanks for your warm work earnestly.

(3) Company Editor-in-Chief: I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: We appreciate for editors and the reviewers' warm work earnestly. According to your suggestions and comments, we have made revision in the paper. If there are any other modifications we could make, we would like very much to modify them and we really appreciate your help. We hope that our manuscript could be considered for publication in your journal. Thank you very much for your help.