

ANSWERING REVIEWERS



Oct 16, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5528-revision1.docx).

Title: Irritable bowel syndrome: The evolution of multi-dimensional looking and multidisciplinary treatments

Author: Full-Young Chang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5528

Dear Mr. Editor-in-Chief:

Thanks for the valuable comments given by the reviewers, now the revision of this manuscript (ESPS Manuscript NO: 5528) has been finished according to their comments.

The text in **red font** is to highlight the changes I have after revision, while the point-to-point responses to the reviewers are listed below:

Reviewer 1:

1. Thanks for your reminding, now all the abbreviations of C-IBS and D-IBS have been changed to IBS-C and IBS-D, respectively.
2. According to your recommendation, a new reference (#35) has been added in the motility part for the supplement (page 7 and 8).
3. Thanks for your updated information, the newly marketed countries are added (page 22).
4. This FODMAP abbreviation is added (page 15 and 26).
5. This new reference (#85) has been added in the gut microbiota part for the additional evidence (page 14).
6. Your suggested subtitle “visceral hypersensitivity” replaces the wrong one (page 10).
7. Figure 1, illness behavior is added in the social factors. The author is really unknown which event among the social factors is necessarily to initiate dysfunction.

Probably, the initiated event is case-by-case variable among the IBS subjects.

Reviewer 2:

The English polishing for my submitted manuscript before publication is indeed welcome

if it is accepted by WJG.

Reviewer 3:

Major comments:

1. As well as the response to Reviewer 2, English polishing is indeed welcome either from publisher or reviewers. In addition, I tried to modify these emphasized points provided by the reviewer, please evaluate whether they are appropriate.

2. Additionally extensive discussion about “biopsychosocial dysfunction” is added.

Please refer to page 6.

3. To address the relationship between genetic, environment and biopsychosocial dysfunction is added. Please refer to page 11.

4. Your recommendation to address peptides and IBS is now added. Please refer to page 12.

5. According to your suggestion, the conclusion is modified again in page 30.

Minor comments:

#1-8, #10-13 and #15-17: Your suggestions of English correction are followed.

#9: The percentage data of MZ and DZ are provided. Please refer to page 11.

#14: The relationship between food and gut microbiota is added. Please refer to page 15.

Reviewer 4:

1. According to your recommendation, a new reference (#75) has been added in the genetic part (page 13) and another new reference (#86) was added in the gut microbiota (page 14) for the supplement.

2. *Full form of some abbreviations need to be given:* These have been corrected with full term.

3. *Last pages of some references need to be mentioned Discussion should be explained in diagram form:* Because the discussion is based on the cited references one-by-one and a biopsychosocial dysfunction diagram is already attached in the first

submission, I don't understand what you mean regarding these two recommendations.

Reviewer 6:

1. Comment: Abstract looks jumpy and it has a piece of everything, i.e pathophysiology, treatment, etc. Answer: Unlike the original study which simply points out a particular issue, the author must address many independent statements about the IBS pathophysiology and treatment in the very limited abstract space of a review article. Accordingly, there is no choice just using many simple and un-related sentences for this purpose.

2. Comment: It is mentioned that gut dysmotility results in pain and disturbed defecation; however, visceral hypersensitivity could be a separate phenomenon. Answer: The reviewer is correct and the author does not deny this statement since there is another subtitle to address it (page 10).

3. Comment: Also it is mentioned "Imbalanced gut microbiota alters epithelial permeability, activates nociceptive sensory pathways in turn leads to IBS". Still it is not clear imbalanced gut microbiota causes IBS or it is seen in IBS as one of the findings. Answer: The author agrees your comment and it is replaced with "may" (page 2).

4. Comment: In genetic section, endocannabinoids are not peptides! Answer: Thanks for your remaining and it is corrected (page 12).

5. Comment: "Interleukin-10 (-1082 G/G) polymorphism accounts for the European IBS population". But based on this meta-analysis high producer IL-10 genotype was associated with a decreased risk of IBS in general and not just in European population. Answer: Thanks for your valuable comment, the author apologizes to provide this mistaken statement and it is corrected following your comment (page 13).

6. Comment: Post-infectious IBS should be separated from microbiota. Role of immune system is missed in the pathophysiology section. Answer: According to your comment, now it is added (page 13-15 and new reference #87).

7. Comment: Gender differences are important to be discussed. Answer: Gender factor has been the main topic regarding epidemiology. It looks beyond the scope of this review

which mainly targets on pathophysiology and treatment. The author apologizes unable to further provide the gender impact.

8. Comment: Motility patterns, such as discrete cluster contractions are important and are missed. Answer: The reviewer may be right, however, there are some publications to indicate the same discrete cluster contractions between IBS patients and controls. Please refer to the following:

A. Small PK, et al. Large-scale ambulatory study of postprandial jejunal motility in irritable bowel syndrome. *Scand J Gastroenterol.* 1997;32:39-47.

Abstract: By means of analysis of variance (fitting factors for channels, meals, and time periods) postprandial contraction frequency was greater in both patient groups compared with normal (constipation-predominant versus normal, diarrhoea-predominant versus normal; $P < 0.001$). In the constipation-predominant cohort, contraction amplitudes were lower (constipation-predominant versus normal; $P < 0.002$). **Discrete cluster contractions occurred with similar frequency and duration in both patient and volunteer groups.**

B. Lee OY. Asian motility studies in irritable bowel syndrome. *J Neurogastroenterol Motil.* 2010;16:120-30.

Text: Therefore, the correlation between DCCs and IBS symptoms remains to be clarified (page 123).

9. Comment: Therefore, to my feeling, some of the discussed materials are not based on extensive and accurate literature review and this seriously affects the quality of the paper. Answer: In my opinion, an IBS review article cannot cite all the worldwide IBS publications. For the knowledge supplement, it is why the similar review will repeatedly appear each year, while the cited references in limited number are not always the same.

10. Comment: In the core tip, the term victim is not suitable for patients with IBS. English still needs revision. Answer: Now this word is deleted. The author has obtained English advice from an expert.

Sincerely yours,

Full-Young Chang, MD.

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