

January 24, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5991-review.docx).

Title: Acupuncture-moxibustion in treating irritable bowel syndrome: How does it work?

Author: Xiao-Peng Ma, Jue Hong, Cai-Ping An, Dan Zhang, Yan Huang, Huan-Gan Wu, Cui-Hong Zhang, Sian Meeuwsen

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5991

Revision has been made according to the suggestions of editor and reviewers. We hope that we have satisfactorily addressed all your comments.

1 Editor comments:

We have provided the following information requested by the editor: running title, authors' affiliations in detail, author contributions, core tip.

2 Below is a list of point-by-point response to each reviewer's comments. The manuscript has been improved according to the suggestions of reviewers.

Reviewer 025261971:

1) I would strongly suggest adding a table briefly summarizing the studies. This would increase the clarity and shorten the length of the article. The text in the current version is too long and is poorly-organized.

Response: It's really a great idea to use a table to summarize the studies. However, it's very difficult to put so many studies into a table. Therefore, instead, we have drawn a chart to show the general concept of this review.

2) The enteric nervous system plays a critical role in the pathogenesis of IBS. However, the current review didn't provide any evidence regarding acupuncture modification of this mechanism. I suggest adding a paragraph. For example, a study published in *Zhongguo Zhen Jiu* by Yang HY et al can be discussed.

Response: We definitely agree that the enteric nervous system plays a critical role in the pathogenesis of IBS. We have added this part into the updated version.

3) A simple schematic drawing showing the anatomic locations of the points used in the review would be useful and helpful to readers.

Response: The drawings have been added.

4) Please briefly explain the terms Ap, Fp and Fz wherever appropriate.

Response: We have explained the terms in the corresponding part of the manuscript: Ap refers to the amplitude of peak, Fp refers to the frequency of peak, and Fz means the average zero-crossing frequency.

5) There are many grammar errors.

Response: We have carefully edited the English language.

Reviewer 02567636:

1) This is a disjointed, rambling and very selective literature review that sets out to review the role of acupuncture and moxibustion in the treatment of IBS. In reality it becomes a discussion of how acupuncture might affect or does affect many systems that might be involved in IBS, both of which are very speculative. So the review is unhelpful. It would benefit from an explanation of what is involved in the delivery of these therapies to IBS patients and then a systematic review of outcomes of those trials.

Response: We are sorry that this article disappoints the reviewer, but meanwhile, we agree that there is a discussion in the relevant field. Just because of the discussion or doubt, it seems more necessary to make clear the current research status. It's also an inspiring comment for our future work. According to the comment, we would like to conduct another research of the delivery of acupuncture and moxibustion therapies to IBS patients.

Reviewer 02529823:

1) This manuscript has some spelling mistakes and grammar problems.

Response: The manuscript has been edited by the language editing company AJE, please see the attached certificate.

2) I would suggest the authors to give a short introduction to acupuncture-moxibustion in the INTRODUCTION section?

Response: The introduction has been added to the corresponding sections.

3) Though acupuncture and moxibustion are often used together, they are different approaches for disease treatment. Whether all the experimental acupuncture conclusions in the manuscript are based on both of them (acupuncture and moxibustion) or each of them? Why they have to use together or separately if necessary?

Response: This is a very valuable question. Indeed, acupuncture-moxibustion comprises both needling and moxibustion therapies, used either separately or together in clinic to treat various diseases. Acupoint is the foundation of the action of acupuncture-moxibustion. Although they stimulate acupoints in different ways, acupuncture through mechanical stimulation, moxibustion through thermal stimulation, they finally produce therapeutic efficacies by giving effective stimulation to acupoints, through which the target organs are regulated. Therefore, acupuncture and moxibustion are often discussed and analyzed together. Current researches majorly focus on the regulatory action mechanisms of acupoints on IBS target organs after the acupoints are stimulated by acupuncture and moxibustion. However, what are the mechanisms of acupuncture-moxibustion in initiating acupoints? What are the differences between acupuncture and moxibustion in the initiation and intervention for IBS? These questions should all remain in our minds for further exploration.

4) Can you supply the explanation about the mechanism of regulation of gastrointestinal motility, visceral hypersensitivity, brain-gut axis, neuroendocrine system and immune system through the acupoints?

Response: Current data demonstrate that the treatment of IBS with acupuncture-moxibustion is closely related to regulation of the gastrointestinal motility, visceral hypersensitivity, brain-gut axis, neuroendocrine system, and immune function. According to TCM theories, acupuncture-moxibustion produces a positive regulating effects by effectively stimulating acupoints and modulating meridian system. Up to date, no research can definitely tell the afferent and efferent pathways through which acupuncture-moxibustion stimulates acupoints and subsequently regulates the gastrointestinal motility, visceral hypersensitivity, brain-gut axis, neuroendocrine system, and immune system. It's already drawn much attention and expects further studies in the future.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, reading 'Ma Xiaopeng' in a cursive style.

Xiao-Peng Ma, MD, PhD

Key Laboratory of Acupuncture-moxibustion and Immunology

Shanghai Research Institute of Acupuncture and Meridian

No.650 South Wanping Road, Xuhui District, Shanghai, 200030, China

Fax: +0086-021-64382181

E-mail: pengpengma@163.com