Format for ANSWERING REVIEWERS

March 15, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8262-edited.doc).

Title: Efficacy of Tandospirone for Patients with Irritable Bowel Syndrome-Diarrhea and Anxiety

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
(1) Reviewer 1:

Q: It is necessary to review spelling (minor). For example, on page 3, the correct is “hitherto” and not “hithreto”.
A: The spelling of “hithreto” to “hitherto” has been revised.

Q: Is there a protocol for registration of international trial?
A: No.

Q: A discussion is relevant but it coud be reorganized. I seggest the following order: 1) answer (brief presentation of results); 2) positioning (background and link between current knowledge and results, interpretation); 3) contribution (clinical application, advice); 4)termination (conclusion, extrapolation, needs for further studies).
A: This suggestion is good. But we think that the existing order of the discussion is also reasonable, so we retain it.

(2) Reviewer 2:

Q: The entire introduction has a lot of repitition (i.e. "IBS is associated with psychological stress, anxiety and depression", also "IBS patients may commonly experience anxiety and/or depression", also "IBS-D patients usually suffer from anxiety") - this should be addressed and the introduction made more succinct.
A: The sentence “IBS patients may commonly experience anxiety and/or depression” has been deleted.

Q: The first reference should be updated.
A: The first reference has been updated.

Q: The Rome-III criteria should be cited after reference 8
A: Reference 12 has been cited to explain the “Rome-III criteria”.

Q: The final paragraph of the introduction should have a more specific aim.
A: The more specific aim has been added in the final paragraph of the introduction.

Q: Can the authors claim this is a study of "safety" if the power was based on efficacy?
A: The power of our manuscript was based on efficacy, and not safety. Only the adverse events of tandospirone were evaluated. It is not suitable to claim this is a study of "safety". So some wordings about "safety study/evaluation" have been deleted or revised to "evaluation of adverse events".

Q: Brief mention should be given of the diagnostic criteria of IBS-D for those not familiar with the Rome-III (this could possibly be given in a supplementary box/table).
A: Brief mention has been given of the "Rome-III criteria of IBS-D" in the part "*Participants*" of "MATERIALS AND METHODS".

Q: Were all the patients diagnosed with an anxiety disorder by a professional psychiatrist?
A: Yes, all the patients with an anxiety disorder were diagnosed by a professional psychiatrist.

Q: The authors should briefly mention/reference the reason for exlcuding those with functional dyspepsia.
A: The symptoms of functional dyspepsia, such as abdominal pain, abdominal distention, belching, heartburn and so on, are overlapping or interactional with the symptoms of IBS-D. This might influence the observation of symptoms and evaluation of therapeutic effect. So the patients with functional dyspepsia were excluded.

Q: Were sexually active women not using brith control excluded to ensure that they weren't pregnant? This is a strange exclusion, as in fact those taking hormone therapy to prevent pregnancy may in fact have milder/less painful periods which may have altered the results.
A: The expression of "sexually active fertile women not taking medically approved birth control measures" is not exact in the manuscript. In fact, the meaning is that we would exclude the participant if she was going to be pregnant in the period of the study. It has been revised in the part of "Participants" of "Materials and Methods".

Q: A brief explanation of the drug pinaverium should be given as not all readers may be familiar with it.
A: A brief explanation of the drug pinaverium has been added in the part of "Study intervention" of "Materials and Methods".

Q: Was this study double blind? If not this should be explicitly stated.
A: This study was single blind, and not double blind. This has been explicitly stated in the text.

Q: How was it determined if patients had missed 5 consecutive days of treatment - did they keep diaries? Patients who missed four consecutive days each week could technically have completed the study - is this correct?
A: All patients were requested to record whether they had drugs daily. The patient who had missed ≥5 consecutive days of treatment in 8 weeks of the study would be withdrawn from the trial. The meaning of "5 consecutive days" is 5 consecutive days "in the whole 8 weeks", but not "each week". We have revised the presentation in the text.

Q: What was the placebo? Did it taste better/worse than the study drug - this could also be an important factor in drug compliance.
A: The overwrap of placebo was the capsule that had a same shape, colour and taste with tandospirone.

Q: Safety: power calculations should be given for the safety study

A: The power of our manuscript was based on efficacy, and not safety. Only the adverse events of tandospirone were evaluated. So some wordings about "safety study/evaluation" have been deleted or revised to "evaluation of adverse events".
In the future, more power calculations about "safety" would be preformed for the safety study.

Q: What was the training given to the data collectors to ensure that data was collected in a systematic and consistent manner.

A: We performed the strict training about collecting data for the data collectors. We also made the scoring sheet for assessing abdominal pain and diarrhea scores and the HAM-A scale sheet for evaluating anxiety degrees. These sheets were concrete but succinct, and easy to be used.

(3) Reviewer 3:

Q: a more informative title of the manuscript should be "Efficacy of tandospirone plus pinaverium compared to pinaverium alone for Patients with Irritable Bowel Syndrome-Diarrhea and Anxiety in a Single-blind Trial".

A: The suggestion is good. But we might not revised the title as above, because the title should be less than 12 words that be requested in "The Revision Policies of BPG for Brief Article".

3 References and typesetting were corrected

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

Sincerely yours,

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