

RE: World Journal of Gastroenterology

ESPS manuscript NO: 31909

Title: Use of selective serotonin reuptake inhibitors and their relationship with Irritable bowel syndrome-a population based cohort study

Feb. 7, 2017

Dear editor, World Journal of Gastroenterology Editorial Office:

Thank you for the decision letter (Jan. 16, 2017) and the reviewer's comments for our above referred manuscript. We have revised the manuscript according to your instructions and responded to the reviewer's comments point-by-point. The red-marked copy of the revised manuscript is attached. We have provided our responses to the reviewer's comments in the following pages.

We appreciate very much again for your review of the revised manuscript and consideration for publication in this outstanding journal.

Yours sincerely,

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Reply to the reviewer's comments:

Reviewers' comments:

This study by Lin et al probes the relationship between SSRI use and the subsequent diagnosis of IBS over a 10-year span, using a national health insurance research database. The data indicate an adjusted increase in HR of 1.74 (P=0.002) for the diagnosis of IBS in patients treated with SSRI.

Strengths: 1. Large numbers since using database. 2. I agree with excluding

IBD and infectious enterocolitis patients. 3. This reviewer recognizes that "Most patients may tolerate the symptoms and not seek out medical advice. This may also lead to the incidence of IBS being underestimated in young individuals." 4. It may be important to consider if "The higher hazard ratio of IBS in individuals with less SSRI exposure time may be due to early onset GI side effects of SSRI that lead to misdiagnosis of IBS by clinical physicians."

Ans:

Thanks for your comments.

Weaknesses:

1. My biggest issue with this paper (like most database reviews) are the limitations with how accurate the EMR reflects what is actually happening in real life. Yes, these medications are being prescribed, but how compliant are the patients being? They do mention this in the second to last paragraph of the discussion.

Ans: Thanks for your comments. We add descriptions about drug compliance in page 8, at lines 23-28. We add this point to the second and third limitations in page 14, at lines 4-6.

2. Similarly, just because there is no IBS diagnosis code prior to the onset of SSRI use, doesn't mean it wasn't there. I.e. physicians don't always code for everything, especially if it is outside of their expertise. I'm sure many psychiatrists don't code for IBS; and I'm sure many internists and gastroenterologists don't code for depression/anxiety.

Ans: Thanks for your comments. We add this points in the fifth limitation in page 14, at lines 7-11.

3. The most important question is that of "chicken and egg." The tone I get from the paper is that the authors are suggesting that SSRI use may predispose or increase the risk for developing IBS. However, IBS could lead to psychological problems, leading to SSRI treatment. The study

would be much more powerful if the authors could show that another class of antidepressants when given to patients with depression do not lead to the subsequent diagnosis of IBS. I suspect the database would allow this important control.

Ans: Thanks for your important comments. We add subgroup analysis of SSRI and non-SSRI users to evaluate the HR of IBS in users of SSRI and other antidepressants (Table 5) in page 11, at lines 12-17, and add discussion about table 5 in page 13, lines 16-21.

4. What is meant by "To ensure the validity of diagnosis, the diagnosis of IBS was defined as more than three times outpatient visits, or more than once during inpatient hospitalization." It seems that mentioning it twice during an inpatient admission is not a strong criterion.

Ans: We revised it as " To ensure the validity of the diagnosis, we included only patients who were diagnosed with IBS (ICD-9-CM code: 564.1) in more than three outpatient visits or more than one inpatient hospitalization. " in page 8, lines 23-26.

5. There are many grammatical errors throughout the manuscript, which is hard to read. I will list some below.

Ans: Thanks for our comments. A professional English editing has been performed by AMERICAN JOURNAL EXPERTS. A language editing certificate was obtained and uploaded.

#### MINOR POINTS

1. The study was observational, not observatory. This is mentioned twice in MS.

Ans: Both observatory has been revised as observational. It has been corrected at page 4, line 8, and page 8, line 9 with red mark.

2. INTRODUCTION: The 3rd sentence is unclear.

Ans: We revised it as “SSRIs are safer and have a more favorable side-effect profile than the previous generations of antidepressants” on page 6, lines 7-8.

3. 2nd paragraph on p.5: Suggested treatments for IBS should be listed as categories, e.g. SSRI's, TCA's, antibiotics, and cGMA agonists, not really specific drug names, and “etc.” should be deleted.

Ans: We revised it as “The suggested treatments for IBS include antispasmodics, antidiarrheal agents, laxatives, prokinetics, probiotics, anxiolytics, SSRIs, tricyclic antidepressants (TCAs), 5-HT<sub>3</sub> antagonists, cGMA agonists, and antibiotics according to each patient's clinical symptoms.” on page 6, lines 9-13.

4. Suggest: Bottom of p.5, “Antidepressants are often used to treat a variety of functional bowel disorders. Tricyclic antidepressants have been proven to offer statistically significant control of IBS symptoms...”

Ans: We have revised the sentence as your suggestion on page 6, lines 29-31.

5. P. 6, generic drug names e.g. citalopram are not capitalized. The American Gastroenterological Association Institute should be capitalized. Same sentence “for patients with IBS, based on...”

Ans: We revised these words as your suggestion on page 7, line 2 and lines 4-5.

6. MATERIALS AND METHODS: 1st paragraph. “We conducted a retrospective observational study on the correlation of SSRI and its possible influence on IBS.”

Ans: We have revised the sentence as your suggestion on page 8, lines 9-10.

7. RESULTS: “The majority of psychiatric disorders leading to a prescription of SSRI include anxiety and major depressive disorders....”

Ans: We have revised the sentence as your suggestion on page 10, lines 8-10.

8. DISCUSSION: "In this study, we demonstrated that IBS in the SSRI user tended to occur in older patients." "A previous global meta-analysis and questionnaire study in Taiwan..."

Ans: We have revised these sentences as your suggestion on page 12, lines 7-8, 10-11.

9. Page 11, "To evaluate the dose effect....within one year and determined the hazard ratio and ..."

Ans: We have revised the sentence as your suggestion on page 12, lines 18-20.

10. Page 12: "Anxiety and depression disorders are associated with GI symptoms, in accordance with a brain-gut interaction."

Ans: We have revised the sentence as your suggestion on page 13, lines 7-9.

11. Page 12: "The communication between CNS..." This paragraph must be reworded.

Ans: We revised the sentence as "the communication between the central nervous system and enteric nervous system appears to be bidirectional" on page 13, lines 9-10.