January 10, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (Manuscript_6540_REVISED.docx).

Title: Rapid improvement in post-infectious gastroparesis symptoms with mirtazapine

Authors: Shinjini Kundu, Shari Rogal, Abdulkader Alam, and David J. Levinthal

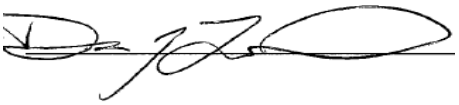
Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6540

I appreciate the opportunity to present our case report. The peer reviewers had useful comments, and the manuscript has now been edited and improved. Please see the section below for our specific responses to reviewer comments and the changes we have made to the manuscript.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*. Feel free to contact me with any questions or concerns.

Sincerely yours,



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RESPONSE TO REVIEWER # 02822905

Major Comments:

1) How were the gastric emptying scintigraphy studies performed, i.e. was a standardized test meal used and images acquired for 4 hours as recommended by consensus guidelines?

RESPONSE TO REVIEWER: Both gastric emptying studies were performed using a standardized test meal. However, the first gastric emptying study performed at an outside hospital was a 2 hour study. The repeat study at our institution was an optimal study performed over 4 hours. These distinctions are now noted in the revised text.

2) Was the patient on any medications at the time, e.g. narcotics, anti-cholinergics, that may have influenced gastric motility? This should be mentioned in the case report.

RESPONSE TO REVIEWER: The reviewer correctly notes that medications themselves can lead to delayed gastric emptying. No narcotics or anti-cholinergic medications were being administered during the initial gastric emptying scan at the outside hospital, but the patient was on a transdermal scopolamine patch during the 4 hour study performed at our center. We have now added additional text to clarify this point.

3) The authors suggest that accommodation reflex may have been impaired in this individual leading to symptoms. Did scintigraphy show any evidence, e.g. abnormal intragastric distribution of food, to support this hypothesis? Furthermore, the authors postulate that mirtazapine may have beneficial effects on accommodation via 5-HT1A receptors. It would be interesting to note if repeat scintigraphy shows an improvement in abnormal intragastric distribution of food after initiation of mirtazapine.

RESPONSE TO REVIEWER: The reviewer raises the good point that a non-invasive measure of gastric accommodation would be useful physiologic data in this case study. One recent report did demonstrate that the data obtained during scintigraphic studies of gastric emptying (obtained every 15 minutes for the first 90 minutes) could be partitioned to obtain proxy measurements of gastric accommodation (Tomita et al. J Gastroenterol Hepatol. 2013 Jan;28(1):106-11). Our center does not currently make such partitioned scintigraphic measures, nor does it collect frequent scintigraphic data from early time points required to make an accurate assessment. Because the data collection was not optimized to assess gastric accommodation, we cannot make the assessment or look for changes in this parameter.

4) What side effects did the patient experience from mirtazapine?

RESPONSE TO REVIWER: The patient did not report any side effects resulting from the addition of the mirtazapine. This detail has been added to the text.

5) Finally, the author's state that because the patient's symptoms improved but did not completely resolve supports their argument that mirtazapine was efficacious. Long-term follow-up of patients with post-infectious gastroparesis has not been published to my knowledge. However, if we extrapolate data from post-infectious irritable bowel syndrome, this statement may not be true. Up to 15% of subjects with post-infectious IBS continue to have symptoms 8-10 years after the initial diagnosis (1,2).

RESPONSE TO REVIEWER: We appreciate the reviewer's comments. We agree that good long term follow up data on post-infectious gastroparesis patients is lacking.

Minor Comments:

1) The references should be reviewed. Specifically, the authors cite reference 14 as evidence of mirtazapine in the setting of cancer chemotherapy.

RESPONSE TO REVIEWER: The reviewer correctly identified an error in citation. The correct citation for this point is reference 10. All citations have now been reviewed and corrected.

2) There are also some spelling errors that should be corrected in the paper.

RESPONSE TO REVIEWER: We have now diligently checked our manuscript to look for and correct errors that escaped detection on the first submission.

RESPONSE TO REVIEWER #00070271

Major Comments:

1) Abstract.- Is very short, the instructions for authors say they should not be less than 200 words.

RESPONSE TO REVIEWER: We have now extended our original abstract (currently 186 words). The author instructions that we have received state a goal of including "an informative, unstructured abstract of no less than 150 words…". Thus, our revised abstract should now be in compliance.

2) Keyword.- I suggest keywords to be reviewed and matching the MeSH terms. Post-infectious gastroparesis is not on the list.

RESPONSE TO REVIEWER: We have removed the qualifier "post-infectious", as it is not included as a MeSH term.

3) Core tip.- This section is missing.

RESPONSE TO REVIEWER: We have now added this section to the manuscript. It is currently 77 words.

4) Introduction.- Some of your references describes properly the incidence of the gastroparesis symptoms and etiology, in order to reach a better approach of the pathology description I recommend to make the proper adjustment.

RESPONSE TO REVIEWER: It is not clear what the reviewer has in mind regarding "the proper adjustment". We cite a few authoritative papers on gastroparesis and other functional stomach disorders. We have opted to leave our introduction in its current form.

5) Case Report.- When you describe the first solid phase gastric emptying study you report the 2 hours results but when the study was repeat after mirtazapine administration you use the 3 and 4 hours results, it would be better if you also describes the 2 hours results to make the reader realize the changes.

RESPONSE TO REVIEWER: We agree that it would be best to compare similar clinical values. Therefore, the revised manuscript directly reports the 2 hour values of both gastric emptying studies.

6) I would like to know if the antiemetic drugs previously used are listed in the correct timing order.

RESPONSE TO REVIEWER: Based on the patient interview and some limited medical records from the outside medical facility, the order of medications as described in our report corresponds roughly to the order in which they were trialed.

7) It would be better if you describe or named the criteria used for the psychiatric diagnosis rejection.

RESPONSE TO REVIEWER: The psychiatry team would make any diagnosis based on the DSM-IV criteria (as was used at the time). We have added this detail to the manuscript for the sake of completeness, particularly given that the DSM-V has now been introduced since the original case occurred.

8) Also I would like to know, which was the nausea scale used? Is it validated?

RESPONSE TO REVIEWER: We used a simple 11-point verbal rating scale (0-10) to quantify the intensity of the patient's nausea. Based on an investigation of the relevant literature, this method appears to be standard for clinical trials involving nausea as a primary measure, and thus it is "valid".

9) When using mirtazapine the patient presents any side effect?

RESPONSE TO REVIEWER: No side effects were reported. We have added this to the manuscript.

10) It would be better if you submit the images of the emptying tests performed for a better appreciation.

RESPONSE TO REVIEWER: We do not have access to the images of the emptying tests from the other hospital, and thus cannot present the comparison.

11) Discussion.- There is a problem at this section, the reference numbers do not indicate properly the origin of some of the paragraph discussed. Along this section there has been made some supposed statement not scientific supported, that I recommend to delete or properly support.

RESPONSE TO REVIEWER: We agree that there was an error in attribution and numbering. These have been corrected in the revised manuscript.

12) References.- None of the references meets the editorial guidelines. In the text there are 18 numbered but in the list there are just 17. Also in the text they are not numbered sequentially and in superscript as the authors rules ask for

RESPONSE TO REVIEWER: We agree that there was a discrepancy in references and formatting in the original submission. This has now been corrected in the revised manuscript.
