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December 24, 2018

Baishideng Publishing Group, Inc.
7901 Stoneridge Drive, Suite 501
Pleasanton, CA 94588

RE: Manuscript Submission 42710

Dear Dr. Wang and Editors:

In reference to our manuscript editor's and reviewers' comments for our submission to the *World Journal of Gastrointestinal Pharmacology and Therapeutics*, we have the following explanations and have made changes in our manuscript accordingly.

Editor's Comments:

1) A background section was added to the manuscript and does not exceed 100 words.
2) An Article Highlights section was added to the end of the manuscript.
3) The references were reformatted, with the addition of PMID and DOI as requested.

Responses to Comments from Reviewer #1:

1. This is a valid point, but we were unable to divide patients by disease activity for a few reasons. The patients at our institution (a tertiary care facility) were seen often in consultation or for a second opinion, and may have been followed locally by another gastroenterologist (or additionally a primary care physician, urgent care physician, or emergency room physician) who was managing intermittent flares of disease activity. Thus, some of the data regarding disease activity was missing. Secondly, it was often difficult to discern disease activity retrospectively because patients may not have had all elements to specify the degree of remission (e.g. symptomatic remission, histologic remission, endoscopic remission, etc.). Thus, we elected to study patients regardless of disease activity. This was noted in the discussion section following the reviewer's comment, in order to highlight this limitation.
2. While the diagnosis of functional gastrointestinal disease was not accompanied throughout its history with a diagnosis of ulcerative colitis in all patients, both

FGID and UC did overlap in patients at some point during the six-year study period.

3. Yes, all opioid medications were used during the ulcerative colitis history. The methods section was edited in response to this comment.
4. This is certainly another valid point, but due to the retrospective nature of the study and the inability to discern the actual indication for opioid use based on prescription monitoring data (i.e. many patients obtained narcotics from other providers outside of our institution, primary care providers, emergency room visit, etc.), we were unable to distinguish between opioid use strictly for pain from ulcerative colitis versus that from FGID. Thus, this is one of the limitations of this study and accordingly, changes were made to the discussion section to reflect the suggestion made by the reviewer.
5. The reviewer is asking a question that relates to the data presented in Table 1. This table shows the differences in patient characteristics when stratified according to the FGID status, and the only statistically significant risk factor among patients with UC/FGID compared to those without FGID was female sex (74% with FGID versus 48% without FGID, P= 0.010). This information was included in the results section. In Table 2, because of the model used by our statistician, FGID was treated as an independent variable and chronic narcotic use and misuse were not studied in the subsets of the UC population with FGID (i.e. FGID was not combined with other variables, but the other variables were excluded in the multivariate logistic regression analysis).

Responses to Comments from Reviewer #2:

1. This is an excellent point and was edited in the manuscript to provide more detail based on this reviewer's comments. Any diagnosis consistent with an FGID as outlined by Rome III criteria (as Rome IV criteria had not yet been published), including both upper abdominal diagnoses (e.g. functional dyspepsia) and lower abdominal diagnoses (e.g. irritable bowel syndrome with diarrhea, constipation, or combination of the two) were included. Patients with symptoms of an FGID without an existing diagnosis made by a clinician were not included as patients with an FGID, as by definition, these are diagnoses of exclusion.

I hope that you will find the revisions to the manuscript and the responses above to be satisfactory, and I thank you for your consideration of publication of this manuscript. Please do not hesitate to contact me if any further clarification or information is needed pertaining to the manuscript.

Sincerely,

Maithili Chitnavis, MD