Dear Editor,

We are submitting our revised manuscript entitled "Chronic Opioids in Gastroparesis: Relationship with Gastrointestinal Symptoms, Healthcare Utilization and Employment" for which the first decision was made by World Journal of Gastroenterology on 2017-08-30 to "Revise the Manuscript".

We would like to thank the reviewers for their comments and valuable suggestions. The manuscript has been edited according to the suggestions of the reviewers. The changes made have been highlighted in the word document uploaded separately.

We have responded to the specific comments posed by the reviewer on a point-by-point basis and incorporated them into the manuscript where necessary.

Response to reviewers' comments:

Reviewer #1:

The authors present an analysis of a large group of patients seen at a tertiary care facility for the evaluation and management of gastroparesis. The manuscript contains new and useful information, particularly related to issues not emphasized in the study, such as the subgroup of patients with chronic pancreatitis and the prevalence of opioid use in this patient group. The study has several important drawbacks that will need to be addressed prior to its acceptability for publication.

Response: We thank the reviewer for the compliments that the manuscript contains new and useful information. We have now given more information on the subgroup of these patients with chronic pancreatitis (see pages 16 and 17 of manuscript). We have also addressed the drawbacks in our study pointed out by the reviewer below. The changes in the manuscript are highlighted in yellow.

The main issue with this analysis is that 43% of the patients receiving opioid therapy apparently were placed on these medications as a result of their diagnosis of gastroparesis. Thus, almost half of the patients receiving opioids and demonstrating increased severity of upper G.I. symptoms including abdominal pain produce a skew in the data analysis when lumping all of the patients receiving opioids into one group and comparing symptoms in those patients with a group of patients having gastroparesis but not receiving opioid therapy. This can be resolved by performing a sub analysis of the group that were on opioid therapy because of their G.I. symptoms and comparing those to patients not taking opioid's and to patients on opioid therapy for other reasons.

Response: The data on opioid use has been clarified in the manuscript. Six (14%) patients were taking opioids only for gastroparesis and/or stomach pain, while another 12 (27.9%) patients mentioned gastroparesis and/or stomach pain amongst the reasons they were taking opioids (along with other indications). The remaining 25 patients were taking opioids for reasons that did not include Gp or stomach pain. Given the relatively smaller sample sizes, it was not be possible to have meaningful additional sub-group comparisons, which can possibly be addressed in future studies with larger sample size.

Additional specific issues with the manuscript:

1. The last sentence of the abstract does not make sense and needs to be rewritten.

Response: The last sentence of the abstract has been re-written (divided in 3 sentences).

2. Introduction paragraph 3. The mechanism by which opioids cause nausea and vomiting should be mentioned.

Response: This mechanism by which opioids cause nausea and vomiting has been added in the 3rd paragraph of introduction (see page 6 of manuscript).

3. Patient recruitment for this study is not clear. Were these consecutive patients seen for the specific diagnosis of gastroparesis? Were questionnaires administered as part of their clinical care? Is this a retrospective review of the questionnaires and other data collected during the clinical visit? It appears from the methods the patients were recruited following their clinic visit. Did they need to sign a consent? There is no statement about IRB approval for the study.

Response: These were consecutive patients seen at our center for the first time with either established diagnosis of gastroparesis (87.9%) or symptoms that were suggestive of gastroparesis (see page 10 of manuscript). The questionnaires were administered for the research project. It is a retrospective review of the questionnaires and other data collected. Subjects were recruited following their scheduled office visit and after informed consent was obtained. The above details and a statement about IRB approval has been included in the manuscript (see page 7 of manuscript).

4. The authors state that the questionnaire utilized was validated. However they should specify that the questionnaire was validated for patients with upper gastrointestinal symptoms, not patients with gastroparesis.

Response: The PAGI-SYM questionnaire has been validated in patients with upper gastrointestinal symptoms of gastroparesis, dyspepsia, and gastroesophageal reflux disease. This has been specified in the manuscript (see page 7 of manuscript).

5. A number of laboratory tests were performed and listed in the methodology. However the rationale for these laboratory tests is not listed. If the tests were irrelevant in regards the current study, they do not need to be listed in the methods section.

Response: The rationale for doing the blood work including TSH, hemoglobin A1c, trypsinogen and cortisol levels has now been mentioned (see page 8 of manuscript), while the other blood tests have been removed from the methodology section.

6. There is a serious problem in the description of the gastric emptying studies in the methods section. The authors state the patients were told to stop medications that can alter gastrointestinal motility 48 hours prior to their gastric emptying scan. Thus, patients on chronic opioid use would have to stop their medications and would be a very high risk for opioid withdrawal. Was a system in place to gradually withdraw patients on chronic opioid therapy prior to the gastric emptying scan? Were patients one of the risk of opioid withdrawal in the consent form?

Response: The patients on chronic opioids were advised to gradually taper off opioids prior to the gastric emptying scintigraphy (GES) so that they were off the opioids for 48 hours prior to Gastric Emptying Scintigraphy (added to page 9 of manuscript, under "Gastric Emptying Scintigraphy"). However, 14 patients were still taking opioids at the time of GES. When we compared GES results of these patients with other chronic opioid users who were not taking opioids at the time of GES, there was no difference in gastric retention at 2 and 4 hours. This has been mentioned in the study (see page 12 of manuscript, under "Gastric Emptying Scintigraphy").

7. At the end of the paragraph on use of schedule opioids, the term "prior" alcohol use is needed to differentiate those patients from patients currently using alcohol.

Response: The data on history of alcohol use includes prior and/or current alcohol use. This has been clarified to differentiate this from current alcohol use only (see page 11 of manuscript, under "Gastroparesis patients on chronic scheduled opioids")

8. The authors emphasize the presence of low cortisol in patients receiving opioid therapy in several places in the manuscript. However, the numbers were small, and differences in the two groups were not statistically significant. Therefore, the references to low cortisol levels in patients receiving opioid therapy throughout the manuscript need to be removed as this finding was not a significant finding.

Response: We have mentioned the rationale for checking cortisol in the ''Laboratory Analysis'' section of Methods (see page 8 of manuscript). However, since the difference in low cortisol level between GpCO and GpNO was not statistically different, we have removed it from the Discussion section.

9. The discussion regarding lack of difference in constipation between the patients using chronic opioids and those that did not is inadequate. If the authors collected data on OTC laxative use, these should be included in the manuscript. The reference to the small number of patients using prescription treatments to prevent opioid - induced constipation should be removed, as the numbers too small to be relevant for the study.

Response: Our questionnaire did not specifically ask about the use of laxatives. We did review their medication list at the time of their first appointment in our center, and mentioned the number of patients who had laxatives/stool softeners listed on their medication list (see page 16 of manuscript, under Discussion). Future studies should look into the prevalence of laxative use in gastroparesis patients taking opioids.

10. The proper term for serum trypsin is serum trypsinogen. These data are interesting. The authors should discuss the sensitivity and specificity of serum trypsinogen for diagnosing chronic pancreatitis. They also do not define the term ″low serum trypsin″ in terms of their cut off for an abnormal serum concentration. Finally, they should note that if the serum trypsinogen is in fact abnormally low, it suggests that these patients have calcified chronic pancreatitis and likely have severe pancreatitis.

Response: We have changed trypsin to the trypsinogen in the text. Sensitivity and specify of serum trypsinogen has been mentioned (see page 17 of manuscript, under Discussion). Cut off for low serum trypsinogen (less than 19 ng/mL) has been included in Table 2. We have mentioned in the text that the patients with low serum trypsinogen possibly had severe chronic calcific pancreatitis (see page 17 of manuscript, under Discussion).

11. In my view, the authors place too much emphasis on the reliability of recall of opioid use relative to the diagnosis of gastroparesis. There should be some mention regarding the efficacy of using recall methods for use of opioids and other medications, otherwise this portion of the results and discussion should be removed.

Response: In the 2nd paragraph under "Gastroparesis patients on chronic scheduled opioids" we have referenced an article that the patients' recall on their medication usage are often be inaccurate (see page 11 of manuscript). Hence, we removed the line mentioning the average duration of opioid use before the onset of symptoms of gastroparesis in about one fourth of GpCO who reported using opioids before their onset of symptoms of gastroparesis. However, we kept the other details, as we feel that some data on the duration of opioid use versus duration of symptoms would be beneficial for the readers.

Reviewer #2: The authors aim to examine the relationship of chronic opioid use on symptoms, healthcare utilization and employment in patients referred for Gp by comparing those with delayed gastric emptying chronically taking (GpCO) or not taking opiates (GpNO). The authors concluded that chronic regular opioid use is present in a significant number (19.3%) of "gastroparesis patients" and these patients have a higher severity of many gastrointestinal symptoms including those of Gp. They also have decreased work productivity compared to non-opioid using Gp patients. This study is based on a well-known GI motility center from where many important gastric emptying studies have been carried out and published. Nevertheless, before reaching the conclusion, there were several limitations needed to be taken into account, in addition to those the authors have mentioned in the discussion section.

Response: We would like to thank the reviewer for appreciating the studies done at our center on gastrointestinal motility disorders. The limitations pointed out by the reviewer have been addressed below.

Major 1. To the reviewer's knowledge, gastroparesis is usually defined as severe delayed gastric emptying, which means the gastric retention more than 35% at 4th hour on standard gastric emptying scintigraphy. However, it seems that the authors defined the gastroparesis as delayed gastric emptying (more 10% retention at 4th hours). Please clarify the definition of gastroparesis?

Response: Gastroparesis is a symptomatic chronic disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction[1]. While the cut-off values to differentiate normal from delayed gastric emptying on gastric emptying

test can vary at different institutes, retention of more than 60% at 2 hours and/or more than 10% at 4 hours has been used in most studies performed on gastroparesis published in the literature that used gastric retention at 2 and/or 4 hours to diagnose gastroparesis[2,3]. Moreover, these cut off values were established in a study on healthy volunteers published by Tougas et al as referenced in our manuscript[4]. Retention over 35% at 4 hours is generally used for severe delays in gastric emptying, and some information on this subgroup of patients has been added to the manuscript (see pages 12 and 13 of manuscript).

1. Parkman HP, Hasler WL, Fisher RS, American Gastroenterological Association. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology. 2004; 127(5):1592–622. [PMID: 15521026]

2. Hasler WL, Wilson LA, Parkman HP, Koch KL, Abell TL, Nguyen L, et al. Factors related to abdominal pain in gastroparesis: contrast to patients with predominant nausea and vomiting. Neurogastroenterol Motil. 2013; 25(5):427–38, e300-301. [PMID: 23414452, DOI: 10.1111/nmo.12091]

3. Cherian D, Parkman HP. Nausea and vomiting in diabetic and idiopathic gastroparesis. Neurogastroenterol Motil. 2012; 24 (3):217–22, e103. [PMID: 22118574, DOI: 10.1111/j.1365-2982.2011.01828.x]

4. Tougas G, Eaker EY, Abell TL, Abrahamsson H, Boivin M, Chen J, et al. Assessment of gastric emptying using a low fat meal: establishment of international control values. Am J Gastroenterol. 2000; 95(6):1456–62. [PMID: 10894578, DOI: 10.1111/j.1572-0241.2000.02076.x]

2. The authors have found that GpCO group have more severe symptoms in many aspects using the statistical significance defined by p value <0.05. However, the authors have compared nearly 40 items. Considering the use of multiple comparison has been performed. The p value for significant difference may need to be adjusted. In addition, how many variables have skewed distribution? It may not be appropriate to express them in mean and standard variation as used in all the compared variables.

Response: We have adjusted the p value using Bonferroni correction while comparing multiple groups. We did not adjust for multiple comparisons while comparing opioid-using gastroparesis patients (GpCO) to non-opioid using gastroparesis patients or GpNO, as our primary aim was proposing a hypothesis (see pages 9 and 10, under "Statistical Analysis"). Some of the previous literature comparing symptom severity in different subgroups of gastroparesis also did not adjust for multiple comparisons[2].

Moreover, we usually adjust for multiple comparisons to decrease the risk of false detection rate. By using a statistically significant p value of <0.05 and doing about 60 comparisons between GpCO and GpNO, there was a risk of about 3 false positive comparisons whereas our data showed 26 statistically significant differences between the 2 groups which is very unlikely to be due to chance alone. Nonetheless, we have added a total symptom severity score on PAGI-SYM questionnaire and this was also statistically higher in opioid using gastroparesis patients (see Table 3).

The continuous variables with skewed distribution have been marked in the tables, these variables are now expressed as median with interquartile range.

2. Hasler WL, Wilson LA, Parkman HP, Koch KL, Abell TL, Nguyen L, et al. Factors related to abdominal pain in gastroparesis: contrast to patients with predominant nausea and vomiting. Neurogastroenterol Motil. 2013; 25(5):427–38, e300-301.PMID: 23414452, DOI: 10.1111/nmo.12091

3. As the authors found that amongst the 43 patients on chronic scheduled opioids, 18 (41.9%) were taking opioids for reasons that included Gp and/or stomach pain. Please clarify how many patients already have the diagnosis of gastroparesis and whether they have been treated. A higher percentage of diagnosed gastroparesis patients may have higher health care utilization and affect the comparison results.

Response: The majority (87.9%) of patients seen at our motility center had an already established diagnosis of gastroparesis and had been treated elsewhere with suboptimal control of their symptoms. The opioid and non-opioid using groups did not differ in respect to an already established diagnosis vs new diagnosis (see Table 2). As mentioned in the manuscript, patients are often referred to Temple University Motility Clinic for severe or persistent symptoms; and our study likely represents a more severe spectrum of the disease. However, this is often the case with most studies done at tertiary care academic centers.

4. Will the opioid drugs be stopped before the GET?

Response: The patients were asked to stop medications that can effect gastric motility at least 48 hours before the gastric emptying test, these included slow taper of opioids as tolerated by the patients which has now been mentioned in the revised manuscript (see page 9 under Gastric Emptying Scintigraphy). However, 14 patients were still taking opioids at the time of their Gastric Emptying Study as mentioned above.

5. The authors have speculated that Gp patients may prophylactically use laxatives. It may help to clarify this point if the authors have the data of current medication used by these patients.

Response: While the questionnaire did not ask specifically about using laxatives and/or stool softeners, we have added some information on these medications based on their medication list in the medical record at the time they were first seen at our motility clinic (see page 16 under Discussion). We may have missed some other patients who may be taking these medications prophylactically. Future studies can look at the prevalence of laxatives in opioid using gastroparesis patients and compare to patients not on opioids more accurately.

6. In this study, the authors found nearly one fourth (23.1%) of GpCO had low trypsin levels, compared to <5% in GpNO. The authors suggested that some of our Gp patients using opioids chronically possibly may had chronic pancreatitis. It would be helpful to clarify the percentage of chronic pancreatitis in the basic demographics.

Response: The information about previously diagnosed chronic pancreatitis has been added to the manuscript. GpCO (7%) were more likely to have history of chronic pancreatitis compared to GpNO (1.3%) p=0.033 (see page 16 under Discussion, and Table 2).

7. Please clarify whether the study was prospective or retrospective? In addition, a statement of ethical committee approval may be needed in the method section. Minor 1. Result, 1st line: it should be 15 months 2. Typos: page 9, 4th paragraph: 41.7%?

Response: It was an observational study where patients filled out a questionnaire on their symptom severity on their first appointment at our motility clinic. They underwent gastric emptying tests and blood work. Subsequently a retrospective review of the collected data was performed (see page 7 under Methods). A statement on approval of the study by Institutional Review Board of Temple University was included in the methods section (see page 7 under Methods). Lastly the duration of the study as well as the typos were corrected.

Reviewer #3:

This is an original contribution describing the clinical characteristics of opioid-associated gastroparesis. The observations are novel and there is no such description in the published literature. A few additional details would be desirable, in order to

strengthen the manuscript and make it maximally informative for researchers in the field and for clinicians:

Response: We thank the reviewer for appreciating our findings as novel that would be a useful addition to the current literature on gastroparesis. We have added the additional details to strengthen our manuscript and make it maximally informative for researchers in the field and clinicians as pointed out by the reviewer, and also responded to the suggestions below.

1. Further detailed information about the gastric emptying results would help the reader understand whether there is a subgroup with markedly delayed gastric emptying, in addition to the report that the mean T1/2 was not significantly different from that of non-opioid gastroparesis.

Response: We have added information on this excellent suggestion by the reviewer. We found that the opioid using patients were not more likely to have severe delays in gastric emptying (>35% retention at 4 hours). Moreover, the opioid using gastroparesis patients with severe delays did not report a higher severity of symptoms compared to the opioid using gastroparesis patients with mild to moderate delays in gastric emptying (see pages 12 and 13 of manuscript).

2. Was there any relationship between degree of delay of GE T1/2 or gastric retention at 4 hours and the dose of opioids in morphine equivalents, appraised as a dichotomous (e.g. < or >30mg/day, or continuous vs. intermittent opioid administration) or as a continuous variable? One way to address this would be to provide a regression or correlation between gastric emptying T1/2 and dose of opioid in morphine equivalent doses

Response: We subdivided the opioid using gastroparesis patients in four quartiles based on their morphine equivalents per day. These groups were compared using ANOVA (see Table 3 added to the manuscript), and individual groups were compared using Student's t-test with Bonferroni correction. We did not find any differences in the severity of delays in gastric emptying in these different groups of opioid using gastroparesis patients. We have also calculated correlation coefficient and there was no significant correlation between morphine equivalents per day, and retention on gastric emptying scintigraphy (see page 12 of manuscript).

3. Please clarify in the stats analysis section whether data in the text section of results are means + SD or SEM

Response: The statistics were initially given as mean ± SD. However, the SD has now been replaced with SEM, while data with non-normal distribution is now mentioned as median with interquartile range.

4. Is there a reason whey diabetics were more likely to be on continuous opioids? Please provide information if available regarding the indications for the opioids. Amazingly, the authors found many patients were on opioids for abdominal pain

Response: The opioid using patients with diabetic gastroparesis more frequently were using opioids for leg pain and/or neuropathy, though the difference did not reach statistical significance possibly due to smaller sample sizes in these subgroups. We hypothesize in the revised manuscript that this may have contributed to higher opioid use in diabetic gastroparesis vs idiopathic gastroparesis (see page 15 of manuscript).

5. The observation that 20% of the patients were on opioids is important; given the tertiary referral practice at Temple University and the national visibility of the senior author, please assess whether there was tertiary referral or Berkson bias. For example, you could identify which patients resided within the catchment population of the medical center and which came from, say, >50 miles away

Response: As mentioned on page 7 in the manuscript, patients are often referred to Temple University Motility Clinic for severe or persistent symptoms; and our study likely represents a more severe spectrum of the disease. However, this is often the case with most studies done at tertiary care academic centers. More than half of our patient population came from outside the catchment area (within 50 miles) of Temple University Hospital, but GpCO and GpNO were equally likely to be referred from outside the catchment area (see Table 2).

6. Do you have any information on marijuana or cannabinoid use? It appears that the non-opioid group were more likely to be using alcohol.

Response: We did not ask patients about marijuana or cannabinoid use, but it is a great suggestion for future studies on patients with gastroparesis. The reviewer correctly pointed that non-opioid users had a trend towards more alcohol use, though the difference was not statistically significant. The wording has been rephrased to reflect this in the manuscript (see page 11).

7. Opioid-associated gastroparesis patients had on average 2* number of bowel movements per week. Is there an explanation for this, such as concomitant medications or over the counter laxatives?

Response: One further analysis of the data, one of the opioid using gastroparesis patients had answered '200' to the number of bowel movements in the past week. On review of medical records, this was more likely to be 20 per week, and was probably a mistake from the patient while filling the questionnaire which subsequently skewed the data. Changing this to 20 gave us the mean of 5.7 bowel movements per week, close to the mean of 5.9 in non-opioid user. Nonetheless, since the number of bowel movements per week were not normally distributed, the results are now expressed as median with interquartile range which were interestingly the same both groups (see Table 5). As mentioned above, our questionnaire did not ask specifically about using laxatives and/or stool softeners, however we have added some information on these medications based on their medication list in the medical record at the time they were first seen at our motility clinic.

Reviewer #4:

Congratulations! Well written manuscript on Gastroparesis. Well presented data. There is a need for information on opioids use in gastroparesis.

Response: We thank the reviewer for appreciating our manuscript including the data presentation. We hope that this information on opioid use in gastroparesis will be useful for clinicians and researchers.

1. Only question I have is if the gastric emptying studies were done on or off prokinetics? You may add this to the manuscript.

Response: The patients were asked to stop medications that can effect gastric motility at least 48 hours before the gastric emptying test, these included prokinetics which has now been mentioned in the revised manuscript (see page 9).

2. Page 8 Line 21. Section on GE scintigraphy please correct normal results as < 60% or equal at 2 hr. and <10% or equal at 4 hr.

Response: This has been corrected in the manuscript (now on page 12 under "Gastric Emptying Scintigraphy").

We would like to thank the reviewers for their valuable suggestions that helped us improve the manuscript.

Asad Jehangir, MD and Henry P. Parkman, MD