

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 35685

**Title:** Chronic Opioids in Gastroparesis: Relationship with Gastrointestinal Symptoms, Healthcare Utilization and Employment

**Reviewer's code:** 01716745

**Reviewer's country:** United States

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2017-08-13

**Date reviewed:** 2017-08-15

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input checked="" type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

Congratulations! Well written manuscript on Gastroparesis. Well presented data. There is a need for information on opioids use in gastroparesis. 1. Only question I have is if the gastric emptying studies were done on or off prokinetics? You may add this to the manuscript. 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.

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**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 35685

**Title:** Chronic Opioids in Gastroparesis: Relationship with Gastrointestinal Symptoms, Healthcare Utilization and Employment

**Reviewer's code:** 02052338

**Reviewer's country:** United States

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2017-08-13

**Date reviewed:** 2017-08-16

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input checked="" type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

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: 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. 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 3. Please clarify in the stats analysis section whether data in the text section of results are means + SD or SEM 4. Is there a reason why 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 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 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. 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?

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 35685

**Title:** Chronic Opioids in Gastroparesis: Relationship with Gastrointestinal Symptoms, Healthcare Utilization and Employment

**Reviewer's code:** 02953383

**Reviewer's country:** Taiwan

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2017-08-13

**Date reviewed:** 2017-08-21

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
		BPG Search:	<input checked="" type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

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. 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?

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.

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.

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

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.

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.

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%?

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**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 35685

**Title:** Chronic Opioids in Gastroparesis: Relationship with Gastrointestinal Symptoms, Healthcare Utilization and Employment

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**Reviewer's country:** United States

**Science editor:** Ze-Mao Gong

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<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
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		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

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. 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. Additional specific issues with the manuscript: 1. The last sentence of the abstract does not make sense and needs to be rewritten. 2. Introduction paragraph 3. The mechanism by which opioids cause nausea and vomiting should be mentioned. 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. 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. 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. 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? 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. 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. 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. 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. 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.