

June 4, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9899-review.doc).

Title: Lubiprostone versus Senna in Postoperative Patients with Opioid-induced Constipation: A Double-Blind, Active-Comparator Trial"

Author: Marciniak

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9899

The manuscript has been revised according to the suggestions of reviewers:

EDITOR COMMENTS	RESPONSE	LOCATION IN REVISED MANUSCRIPT
RESULTS (no less than 120 words): You should present P value where necessary and must provide relevant data to illustrate how it is obtained, e.g. 6.92 ± 3.86 vs 3.61 ± 1.67 , $P < 0.001$;	Editor recommendations were addressed and we have Included P values and relevant data where necessary.	Abstract
Please provide the "Highlighted contents" here, which is a necessary content.	Highlighted Contents were added to the manuscript, as per instructions just prior to the references.	
REVIEWER 1	RESPONSE	LOCATION IN REVISED MANUSCRIPT
The authors intend to investigate lubiprostone versus	We thank the reviewer for their comments.	

<p>Senna in postoperative opioid-induced constipation and they concluded individuals using either lubiprostone or senna showed improvement in symptoms of constipation and quality of life. Most participants in each of the treatment groups required additional medications to control symptoms, and also demonstrate that more than one medication may be required for control of constipation symptoms for the study population. These results would have potential benefits to the physicians who are interested in this area and valuable to be documented in the literatures.</p>		
REVIEWER 2	RESPONSE	LOCATION IN REVISED MANUSCRIPT
<p>The study compares the activity of senna and lubiprostone in the treatment of post-operative opioid induced constipation. The study is interesting but the text can be improved. Some suggestions: Line 4 and in the text delete “active comparator”</p>	<p>“Active Comparator’ is included in the title and the text to distinguish this study from a double blind trial with placebo. We do not see any information that is duplicative. As such, we believe this is important information to include and thus have not deleted. We respectfully request that perhaps the reviewer explain why this piece of information for the reviewer be deleted.</p>	
<p>Line 35 delete “measures”. Add ”treated with opioids”</p>	<p>This sentence was modified as requested to state: “To investigate the efficacy of lubiprostone compared to senna on bowel symptoms and constipation in post-operative orthopedic patients treated with opioids”.</p>	<p>Line 35</p>
<p>Line 46 add “(FIM)”</p>	<p>(FIM) was added as requested after Functional Independence Measure.</p>	<p>Line 46</p>

Line 73-75: Change in : Constipation is frequent in post operative orthopedic patients treated with opioids”	The sentence at Line 73-75 was changed as requested.	Line 89
Line 76 Delete one of “comparing” add “opioid induced” before constipation	This sentence was changed as requested to “There is very limited information comparing the efficacy and safety of pharmacologic interventions for opioid-induced constipation “	
Line 79-80 delete” in the CPac-Sym and Pac –Quol and However”	Deletions to these sentences were made as requested	Line 95
Tables 3 and 4 (Gastrointestinal symptoms and Bowel Movements) can be deleted.	The reviewer requested deletion of the tables and then summarizing the data as median and percentiles. As there is a great deal of content that would then be in text format, we feel that this would be more difficult for the reader. As an alternative, Tables 3 and 4 are kept but we have reduced information in Table 3.. We hope that the editor finds this alternative acceptable.	Table 3
Line 345 Now table 3	Please see above.	
Lines 362-375 are repetitive of figure 1 . Please delete what is repetitive.	Repetitive information was deleted, and a sentence was added referring the reader to Figure 1	Line 450
Line 389 Please summarize the data of the deleted table 3 in the text as median and 25-75 percentiles.	Please see above.	
Place the activity data on Rehabilitation (lines 375 386) before the adverse events (line 343)	This paragraph was moved to the location requested by the reviewer.	Line 407
Line 432 add-SYM and –QOL questionnaires.	-SYM and _QOL were added to the sentence as requested.	Line 528
REVIEWER 3		
1. It is not clear if patients with chronic constipation were enrolled or not in the study. Please, state that clearly in	Patients with chronic constipation were not excluded from this trial. We did however	

<p>Materials and Methods section. Moreover, this should be part of the Discussion.</p>	<p>assess for differences in constipation symptoms and PAC scores at baseline and groups were generally comparable. As noted in the manuscript as well as the tables. Information regarding this as a limitation was already present in the discussion.</p>	
<p>2) due to the age of the patients enrolled it is highly probable that several medications were used by the subjects during the trial. These latter might influence the efficacy of the medications studied. The author should at least provide data that between the two groups there were no differences in terms of predisposing conditions.</p>	<p>Indeed we agree that medications other than opioids may contribute to constipation however as many medications have this as a possible side effect and there is greater variability within patients as to such effects (and the degree of this effect) from specific medications, this would be extremely difficult, if not impossible to assess between groups. For this reason we chose to assess symptoms and scores at baseline, and there were generally no significant differences between groups at baseline as we note above.</p>	
<p>3. Statistical section: lines from 274 to 289 might better fit in the Material and Methods sections. I kindly suggest removing them from the original section.</p>	<p>This section was relocated to Material and Methods as requested.</p>	
<p>4. Although not statistically significant, the morphine equivalents daily dose in the two groups seems to be relevant from a clinical point of view (line 318, page 13). The author might consider adding a sentence about that in the discussion.</p>	<p>As stated in the text and noted by the reviewer, there were no statistical differences between the groups in total opioid doses. Of note there is a large standard deviation as two subjects in the lubiprostone group were taking very high doses of opioids. Thus this perceived difference noted by the reviewer between the groups is likely really not.</p>	

<p>5. Moreover, have the authors' data about a potential direct relation between opioid dose (daily or cumulative) and severity/onset of constipation?</p>	<p>Data was compared by groups as to differences in opioid doses at study onset and during the trial to assure the two groups were equivalent at baseline and during the trial and no differences were found. Though what the reviewer describes is of interest, it was not the purpose of this trial to assess how opioid dose might impact constipation.. In addition, it would not be possible to assess onset of constipation as these patients were admitted with the constipation already present.</p>	
<p>6. Can the author provide more information about the rescue laxative medications that part of the Study population received?</p>	<p>Rescue medications used by subjects in this study included milk of magnesia, polyethylene glycol, magnesium citrate, lactulose and suppositories. This information has been added to the manuscript for clarification.</p>	
<p>7. lubiprostone and senna have different manufacturing costs. The authors should take this into consideration in their costs/benefits analysis and discuss it in the manuscript. Therefore, according to their results, lubiprostone should not be recommended as a valid option for transitory constipation induced by opioid intake.</p>	<p>The reviewer is indeed correct in that charges to the institution for these products differ. The purpose of this study however was not a cost benefit analysis and thus we did not collect all cost information on the subjects. As would be required for such a discussion. A sentence was added to the discussion regarding cost however: "Additionally, although effectiveness did not differ, costs do differ for the two medications evaluated in the present study in that senna is available as a generic medication and thus less</p>	<p>Line 519</p>

	costly; A full cost benefit analysis was not the performed for this study, however.”	
REVIEWER 4	RESPONSE	LOCATION IN REVISED MANUSCRIPT
1. Was pre-operative opioid use an exclusion criterion	Preoperative opioid use was not an exclusion as the surgery which the subjects underwent was often required for control of painful conditions, which might require opioids such as osteoarthritis or spinal stenosis	
2. Were the post-operative diet and ambulation protocols identical in both groups?	All subjects reviewed 3 hours per day of therapy at least 5 days were week, and were on general diets.	
3. Was pre-operative constipation an exclusion criterion?	Same comment as above. Please see response to reviewer 3 above.	
REVIEWER 5	RESPONSE	LOCATION IN REVISED MANUSCRIPT
1. This study addresses an important clinical issue. It investigated the efficacy of lubiprostone-based new therapy for opioid use-associated constipation in post-operative orthopedic patients, primarily in a geriatric population. It appears that the new drug did not show better efficacy than the conventional senna. My suggestions for revisions are as follows: 1) As noted by the authors, the sample size in this study was too small limiting the necessary power required to reach the above conclusion. This needs to be addressed, at least emphasized in the discussion	As noted by the reviewer, this study was undertaken to address a commonly encountered clinical issue. We performed a power analysis as described in the statistical methods section to determine the sample size that was used for this study. Sample size limitation was already present in the limitation section of the discussion.	
2. The results were obtained from a specific patient population but the current title of the manuscript did not reflect this important information.	Information on the population study was added to the title of the study as requested: “Lubiprostone versus Senna in Postoperative	Title

	Orthopedic Surgery Patients with Opioid-induced Constipation: A Double-Blind, Active-Comparator Trial"	
3. Constipation is common in non-opioid user, non orthopedic, general geriatric population. Was there any such patient being included in this study? If so, then the authors need to determine whether those prior constipated patients were appropriate to be excluded or included.	Subjects were compared at baseline as to the degree of constipation symptoms and there were generally no significant differences between the two groups at entry into the study, as described in the text and in the manuscript..	

We thank you and the reviewers for your suggestions, and hope that you find these changes satisfactory. Please contact me if you have any further questions.

Sincerely,

Christina Marciniak MD