

November 7th, 2015

Dear Editor,

Please find enclosed the edited manuscript in word format (file name: **211136** with track changes.doc).

Title: Efficacy and Safety of Laxatives Use in Geriatrics – A mini review.

Authors: Manhal Izzy, Anju Malieckal, Erin Little, Sury Anand

Name of Journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

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The manuscript has been improved by updating the format, making changes to the title and different sections of the manuscript, and making revisions according to the following suggestions of reviewers. Please see the attached revised manuscript and see our answers below.

A. Reviewer one:

1. The introduction section needs a brief discussion on the similarities and differences between symptoms of chronic idiopathic constipation (CIC) and irritable bowel syndrome-constipation (IBS-c) as these two functional disorders share common symptoms.

Answer: A paragraph was added as recommended.

2. Emphasize more on the recent treatment options for CIC and discuss their efficacy and adverse effects. Since, diarrhea and nausea are most common symptoms in these newer treatment options, ~~it could be useful to compare the efficacy vs adverse effects of these modalities.~~

Answer: Given the limited data on the use of the recent agents in geriatrics, we could not elaborate on their efficacy and safety in these populations beyond what is mentioned in the literature. The focus of this paper is to discuss the outcomes of prior controlled clinical trials that were done using oral laxatives in geriatric populations who have chronic constipation. We understand that there are trials done/being done on new agents in general population but this does not mean that we can apply the results to special populations like geriatrics especially in view of the results that we showed in this review with other laxatives where geriatrics can have different response to certain laxatives than general population.

3. Guanylate Cyclase-C activators such as linaclotide and plecanatide are also chloride channel activators but these are activators of CFTR. Lubiprostone is predominantly an activator of chloride channel type 2 (ClC2). Hence, separate sub-headings for chloride channel activator and GC-C might be confusing Classification.

Answer: The classification was reorganized according to the reviewer's comment and according to the recent ACG chronic constipation task force statement (2014).

4. The section describing emerging treatment is an important section of the review and it needs to be elaborated further to include drug candidates that are currently in advance stages of clinical development.

Answer: This section is only a supplement to our article because the scope of our article as mentioned before is to review the safety and efficacy of the already existing treatments among geriatrics based on prior controlled clinical trials. Since none of the emerging treatment was studied in geriatrics, we could not elaborate on their safety and efficacy in this group. This review

is not intended to comprehensively discuss the efficacy and safety of laxatives that are under development and may or may not be used in geriatrics in the future.

5. There have been several recent reviews on treatment options for CIC and IBS-C. These review articles could be referred to include newer developments in treatment options. A PubMed search needs to be performed.

Answer: As stated in the inclusion criteria, this review focuses on controlled trials that were done for treatment of chronic constipation in geriatrics. Treatment approach for IBS-C is beyond the scope of this review. Please refer to our answers for question 2 and 4, as well.

6. Review needs a careful reading to improve language and correct grammatical and spelling errors.

Answer: Language improvement as well as grammatical and spelling review and revision were done

B. Reviewer two:

This review has some limits. The authors did not distinguish:

- 1) IBS with constipation from functional constipation (see Rome criteria).
- 2) Secondary constipation associated to systemic diseases (diabetes, renal failure, connectivites, etc...) from primary constipation and
- 3) Transit constipation from defecatory disorders.

Answer: This review is not intended to discuss the pathophysiology and causes of all conditions that can possibly cause constipation besides chronic idiopathic constipation (ex: systemic illness, defecatory disorders, etc) and their treatment (ex: treating the underlying illness, biofeedback, etc). We briefly mentioned the causes of constipation besides chronic idiopathic constipation and IBS-C because the intent of this review is to discuss efficacy and safety of the oral pharmacologic therapy for chronic constipation.

- 4) Laxatives from colokinetic drugs.

Answer: Colokinetic drugs (ex: Prucalopride) are still classified as laxatives as per the major gastrointestinal textbooks (ex: Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 10th ed) and therefore, there is no need to differentiate them from laxatives.

- 5) In addition, some side effects of laxative drugs are not underlined: * melanosis coli * bloating and flat with PEG etc.

Answer: In our study, we focused on the side effects encountered in geriatric populations studies. Therefore, there might be some side effects that we did not list but that was because they were not appreciated in the reviewed controlled studies among geriatrics.

- 6) Finally, the authors dont say that : *the increase of constipation with age is more pronounced for male than female patients (Werth, B.L., K.A. Williams, and L.G. Pont, A longitudinal study of constipation and laxative use in a community-dwelling elderly population. Arch Gerontol Geriatr. 60(3): p. 418-24).
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Answer: This information was added to the introduction.

- 7) The respective place of oral drugs and enema in the treatment of constipation.

Answer: This review discusses the oral pharmacologic treatments for chronic constipation and is not intended to discuss per rectal therapies.

Sincerely yours,

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