

Dear Reviewers,

Thank you for taking the time to review our manuscript. We appreciate your valuable suggestions and recommendations. We have addressed them in a point-by-point fashion below. The changes are reflected in the manuscript and are marked red for your convenience. We hope the manuscript was revised adequately and can be further considered for publication in the *World Journal of Gastroenterology*.

Reviewer Comment #1.1:

“In this study, Turshudzhyan et al. reported a comprehensive review for the indication and awareness of long-term proton pump inhibitor (PPI) usage. This study is important because the widespread use of PPI therapy in clinical practice. Both physicians and patients should know the indication and side-effect of PPI therapy by an evidence-based medicine. I have some comments: 1. In the introduction section, authors mentioned “Especially as some reports claimed that improper long-term PPI use has risen significantly in the last decade with some data suggesting that only half of patients on PPI therapy had an appropriate indication “. Could authors give more information or definition for the “long-term” duration of PPI usage? According to the reimbursement guideline of health insurance in some countries, most patients with GERD or peptic ulcers take PPI for 3-4 months and patients with H. pylori eradication takes PPI for 7-14 days. How long duration of taking PPI could be recognized as long term? 6 months or more than one year?”

Response #1.1:

Thank you for your question. There is no standardized definition of long-term therapy, however, the most recent ACG guidelines from 2021 [20] on GERD management do suggest starting a more thorough work up, initially with an EGD followed by a pH monitoring if patients have either incomplete relief of symptoms or if symptoms recur after 8-weeks of therapy. For the purposes of defining long-term, we will include this diagnostic approach from the ACG 2021 GERD guidelines [20] in the manuscript.

Reviewer Comment #1.2:

“2. In the section of H. pylori eradication guideline, “However, if found to be positive, treatment options should be offered.” Does the test of “found to be positive” mean H. pylori test or patients’ symptoms?”

Response #1.2:

Thank you for your question. Yes, if patients are found to be H. pylori positive, they should be offered treatment.

Reviewer Comment #1.3:

“3. In the section of clinical indications, authors mention “While PPIs are considered for gastroprotection for patients on NSAID therapy, steroids are not an indication to start PPIs [17].” But in the section of NSAID use, authors mention “PPI therapy is indicated in NSAID users at risk for GI bleeds which includes those on high dose NSAIDs, age greater than 65 years, prior history of ulcers, and/or concurrent use of antiplatelets, anticoagulants or corticosteroids [30,31].” Does it mean PPI therapy is indicated only in patients who are concurrent use of NSAID and corticosteroids, but not indicated in patients who take only (high dose) corticosteroids?”

Response #1.3:

Thank you so much for your question. Scarpignato et al. [17] as well as ACG Guidelines for Prevention of NSAID-Related Ulcer Complications [30] state that concurrent use of NSAIDs and steroids is of concern and needs gastroprotection. Scarpignato et al. [17] specifically state that steroid therapy does not require gastroprotection unless it is used in combination with NSAID therapy. There was a systematic review of RCT done by Narum et al (please see reference below) which did indicate increased risk of peptic ulcer bleeding in patient taking corticosteroids, but statistically significant difference was only seen in hospitalized patients on brief courses of steroids and not routinely seen in ambulatory patient population, which is the focus of this review. We will add this reference to clarify this distinction between inpatient and outpatient PPI use in patients on steroid therapy.

[18] Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. *BMJ Open*. 2014;4:e004587. doi: 10.1136/bmjopen-2013-004587.

Reviewer Comment #1.4:

“4. In the section of drug-drug interactions, authors may add the awareness of concurrent use of direct-acting antivirals (DAAs) and PPI in the patients with viral hepatitis C. Adjust the regimens of DAAs or PPI may be needed when treating patients with HCV.”

Response #1.4:

Thank you for your recommendation. We expanded our drug-drug interactions section to include PPI interaction with direct-acting antivirals (DAAs). We hope this will help

increase awareness of this important drug-drug interaction. We used the following reference to support it, which was added to the reference list:

Wijarnpreecha, Karn et al. "Efficacy and Safety of Direct-acting Antivirals in Hepatitis C Virus-infected Patients Taking Proton Pump Inhibitors." *Journal of clinical and translational hepatology* vol. 5,4 (2017): 327-334. doi:10.14218/JCTH.2017.00017

Reviewer Comment #1.5:

"5. In the section of Strategy 4: Looking for Alternative Options, authors may add the statement about the new drug, potassium-competitive acid blockers (PCB), such as Vonoprazan fumarate, in the treatment of GERD."

Response #1.5:

Thank you very much for this recommendation. We expanded our Strategy 4 section to include a brief discussion of this new drug, potassium-competitive acid blocker (PCB). We used the following reference to support it and it will be added to the reference list:

Rawla, Prashanth et al. "Potassium-competitive acid blockers - are they the next generation of proton pump inhibitors?." *World journal of gastrointestinal pharmacology and therapeutics* vol. 9,7 (2018): 63-68. doi:10.4292/wjgpt.v9.i7.63

Reviewer Comment #1.6:

"Minor correction: 6. "H.pylori" should be corrected into " H. pylori" (add one space between H. and pylori)."

Response #1.6:

Thank you for this correction. We added one space into "H. pylori" throughout the manuscript and marked changes in red for your convenience.

Reviewer Comment #1.7:

"7. In the section of Dementia, please spell or explain the text "AB plaques"."

Response #1.7:

Thank you for this correction. We explained the AB plaques in Dementia section as "deposits of the β -amyloid peptide".

Reviewer Comment #1.8:

“8. The abbreviations in the table should be explained in the footnote below every table.”

Response #1.8:

Thank you very much for this recommendation. We added abbreviations to the footnote below every table. Changes are marked in red for your convenience.

Reviewer Comment #2.0:

“The authors provided a comprehensive review of indications, guidelines, and risks of PPI. This is a very well-written review article, but please consider the following suggestions. Minor comments: The newly developed potassium-competitive acid blocker (P-CAB) has been reported to be superior to PPI in the treatment of reflux esophagitis and H. pylori eradication. P-CAB is a new drug with a short history, so there is not much evidence, but it is likely to become more important in the future. Please consider introducing it in this review, along with some papers on P-CAB. I think that would make this a more in-depth review paper.”

Response #2.0:

Thank you for your feedback. We added and expanded on this new therapy briefly in Strategy 4 section. We provided a brief mechanism of action and highlighted its dose-dependent properties.

Editor-in-chief comment:

“The author(s) must include the keyword “proton pump inhibitor” in the manuscript title. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. In order to respect and protect the author’s intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the

figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable."

Response to the Editor-in-Chief:

Thank you very much for your feedback. We expanded the title PPI abbreviation to now say "Proton Pump Inhibitor". Figure 1 will be submitted separately as an editable Power Point file, per your request. It is original to this paper, so it does not require copyright. We modified tables to fit the three-line-model.

Thank you again so much for your consideration of our manuscript for publication. We hope we were able to satisfactorily address reviewers' and editorial comments and that manuscript is now suited for publication at the World Journal of Gastroenterology. Please let us know if there are any questions or concerns regarding this revision.

Respectfully,

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