

## PEER-REVIEW REPORT

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

**Manuscript NO:** 47641

**Title:** Proton pump inhibitors use increases hepatic encephalopathy risk: A systematic review and meta-analysis

**Reviewer's code:** 02462321

**Reviewer's country:** Italy

**Science editor:** Ruo-Yu Ma

**Reviewer accepted review:** 2019-03-21 08:12

**Reviewer performed review:** 2019-03-23 14:00

**Review time:** 2 Days and 5 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input checked="" type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

Comments on "PPI use increases hepatic encephalopathy: A systemic review and meta-analysis". WJG. By Ma YJ et al. The AA analyzed 7 studies with 4574 pts in a meta-analysis and found a significant association between PPI use and HE risk with a

HR of 1.49, with a moderate heterogeneity among studies and no evidence of publication bias. They conclude that PPI use increases HE risk by 49% in cirrhotic patients. This is an interesting study that needs some clarifications, because of relevant clinical importance. Major Comments As it is universally accepted, duration and dose of PPI treatment are, generally, essential to inducing unwanted side-effects. Hepatic encephalopathy can be rated in different stages. The AA must do an effort to specify, as long as it is possible from the published studies (or at least address the problem): 1)Number of episodes and level of HE (subclinical, moderate, pre-coma, coma?) 2)Mean Minimal Duration of PPI treatment necessary to induce HE ( and which level of HE) Minor Comments -AM > AIM (title) -In Results section, Studies characteristics: Studies was published > were published L.L.

## INITIAL REVIEW OF THE MANUSCRIPT

### *Google Search:*

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

### *BPG Search:*

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

## PEER-REVIEW REPORT

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

**Manuscript NO:** 47641

**Title:** Proton pump inhibitors use increases hepatic encephalopathy risk: A systematic review and meta-analysis

**Reviewer's code:** 00061695

**Reviewer's country:** France

**Science editor:** Ruo-Yu Ma

**Reviewer accepted review:** 2019-03-21 11:44

**Reviewer performed review:** 2019-03-23 15:27

**Review time:** 2 Days and 3 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input checked="" type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input checked="" type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

The piece is simple, concise and clear, results are robust and clinically relevant.  
introduction a) I'm not happy with the first paragraph.(this is my only major request  
for changes) The main issue is not about the indications Proton pump inhibitors (PPIs)



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and their benefits but their growing prescription, one of the world's most frequently prescribed medications, due to growing incorrect use (indication as well as duration). Moreover reporting bias in published trials and marketing cannot be overlooked: emphasis on positive results while negative results are understated. b) for the second paragraph b1) please change the beginning "Emerging » by Accumulationg. b2) add to the list of harms 'Chronic Kidney Disease" Discussion Add a short paragraph about -need for measures to promote the rational use by regulation authorities -need for improving clinicians' concern for benefit/harm ratio -need for pharmaco epidemiological studies Reference Cite doi: 10.1053/j.gastro.2017.04.047

#### INITIAL REVIEW OF THE MANUSCRIPT

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- ☐ Plagiarism
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## PEER-REVIEW REPORT

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

**Manuscript NO:** 47641

**Title:** Proton pump inhibitors use increases hepatic encephalopathy risk: A systematic review and meta-analysis

**Reviewer's code:** 00004403

**Reviewer's country:** Italy

**Science editor:** Ruo-Yu Ma

**Reviewer accepted review:** 2019-03-24 16:53

**Reviewer performed review:** 2019-03-25 11:20

**Review time:** 18 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input checked="" type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

The study is well done and methodologically rigorous. This reviewer has only two minor requests to the authors: - They should add to the study characteristics how many studies were observational and retrospective or prospective and controlled, because the



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former have a significantly lower clinical meaning. - In the discussion the authors should report that the use of PPIs must be banned in patients with cirrhosis or portal hypertension, because there is no reason for administering these drugs in hepatic diseases, as clearly stated in many recent papers (for instance Savarino V et al, Dig Liver Dis 2018; 50:894-902). This is the only way to prevent hepatic encephalopathy in cirrhotic patients taking PPIs.

#### **INITIAL REVIEW OF THE MANUSCRIPT**

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- ☐ No

##### ***BPG Search:***

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- ☐ Plagiarism
- ☐ No

## PEER-REVIEW REPORT

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

**Manuscript NO:** 47641

**Title:** Proton pump inhibitors use increases hepatic encephalopathy risk: A systematic review and meta-analysis

**Reviewer's code:** 00036194

**Reviewer's country:** Australia

**Science editor:** Ruo-Yu Ma

**Reviewer accepted review:** 2019-03-22 05:59

**Reviewer performed review:** 2019-03-27 02:13

**Review time:** 4 Days and 20 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
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<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
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publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

Introduction Para 1: PPIs are used to prevent NSAID ulcers not what you have stated  
PPIs are not useful for functional dyspepsia Introduction Para 2: HE is secondary to  
hepatic failure, not cirrhosis per se. Results may be



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skewed, not restricted as you stated Introduction Para 3: You are not looking at cirrhosis, just HE Methods: Most studies have been excluded and only 7 included. You give the exclusion characteristics but it would be helpful, seeing nearly all studies were excluded, to know how many were excluded for each exclusion criterion. Methods: Is visualisation the appropriate method to determine publication bias?

#### **INITIAL REVIEW OF THE MANUSCRIPT**

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