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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 51784

Title: Liver Injury Induced by Paracetamol and Challenges Associated with Intentional and Unintentional Use

Reviewer's code: 00504935

Position: Editorial Board

Academic degree: BPharm, MPhil, PhD

Professional title: Professor

Reviewer's country: Pakistan

Author's country: United States

Reviewer chosen by: Artificial Intelligence Technique

Reviewer accepted review: 2019-10-16 07:33

Reviewer performed review: 2019-10-16 07:38

Review time: 1 Hour

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 checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input 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



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Acceptable

Thank you for your time and consideration.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 51784

Title: Liver Injury Induced by Paracetamol and Challenges Associated with Intentional and Unintentional Use

Reviewer's code: 03477174

Position: Peer Reviewer

Academic degree: MD

Professional title: Associate Professor

Reviewer's country: Turkey

Author's country: United States

Reviewer chosen by: Ruo-Yu Ma

Reviewer accepted review: 2019-10-21 09:03

Reviewer performed review: 2019-10-29 08:02

Review time: 7 Days and 22 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 (High priority)	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Accept (General priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Minor revision	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish		<input type="checkbox"/> Rejection	<input type="checkbox"/> Advanced
			<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

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I have to say this first, this is a good review and well design. However, I am sorry to say that recently there are published enough novel studies and reviews on this topic in the literature. Therefore, I do not believe that this article will contribute to the literature.

Thank you for your time and consideration.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 51784

Title: Liver Injury Induced by Paracetamol and Challenges Associated with Intentional and Unintentional Use

Reviewer's code: 00002314

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Professor

Reviewer's country: Italy

Author's country: United States

Reviewer chosen by: Ruo-Yu Ma

Reviewer accepted review: 2019-10-21 14:40

Reviewer performed review: 2019-10-29 22:34

Review time: 8 Days and 7 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 (High priority)	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Accept (General priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Minor revision	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> Advanced
			<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

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This manuscript is a nice overview of hepatotoxicity induced by paracetamol. In general, it is well written and easy to follow, but in my opinion it is a bit disappointing because it does not fulfill the expectations raised by the title "A Clinical and Mechanistic Update". - What is the novelty of this manuscript and how can it be helpful to the clinician? The authors should try to be convincing in identifying what this paper adds to the existing literature. For instance, discussing the different size of the problem (i.e. liver toxicity/failure after suicidal attempts) in different countries could provide added value. A table with data could help. - A clinician's interest might be captured more easily if practical management of different clinical cases of liver toxicity were discussed in more detail with flow charts. The use of nomograms (e.g. the Rumack-Matthew nomogram) is only briefly mentioned whereas this part should be more critically discussed. The clinician's main conclusion can be very difficult to grab because of the lack of illustrations/flow charts? Minor points - the maximum adult oral dose of paracetamol: it has remained 4 g daily only in some countries. In some other EU countries, it was reduced to 3 g daily. Please check, and in case provide a brief analysis. - structural formulas could help in the graphical pathways of metabolism. - I noticed some typos.

Thank you for your insightful comments. We address your concerns as outlined below.

In regards to discussing the different size of the problem:

A summary of paracetamol-induced acute liver failure has been added to the clinical outcomes section of the paper (included below), as well as a Table (labeled table 2) comparing cases of ALF, mortality and transplant outcomes among different countries.

Outcomes of paracetamol overdose have been reported from numerous countries. A study from Australia reported over 440 deaths from paracetamol in combination with codeine from accidental overdose, with roughly 25% of these cases also involving other sedating medications, such as antihistamines. While paracetamol has been the main cause of DILI in the United States and the England, it is less common in other European countries, such as Portugal and Germany, only making up roughly 10% of ALF cases according to the European Liver Transplant Registry (ELTR) database. In part, this could be from the increased usage of paracetamol intake in the United States in



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comparison to European countries. A summary of clinical outcomes from paracetamol-induced acute liver failure can be found in Table 2.

For practical application of the nomogram, more information was added to the Rumack-Matthew nomogram section of the review, shown below.

If the time of ingestion is unknown but within 24 hours, the earliest possible time of ingestion should be estimated and plotted on the nomogram to see if treatment with NAC should be initiated (i.e. if above the treatment line). The use of the nomogram should be avoided until four hours or more after ingestion as the levels may be misleading during this timeframe from the point of acute ingestion and not be an accurate predictor of toxicity. ... If medication review reveals co-ingestion with opioids or anticholinergic medications, the post-ingestion level should be checked at 4 hours and repeated at 6 hours post-ingestion if the initial level falls below the treatment line to account for possible delay in maximum serum concentrations of paracetamol.

A flowchart was also added to improve readability as suggested, labeled Figure 3.

For the minor points:

The following has been added to the paper in regards to paracetamol dosing:

Alternatively, dosing guidelines from drug inserts in European countries recommends a maximum of 3,000 mg of paracetamol in older adults either <50 kg or in those >50kg with additional risk factors for hepatotoxicity.

INITIAL REVIEW OF THE MANUSCRIPT

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BPG Search:

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Plagiarism

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 51784

Title: Liver Injury Induced by Paracetamol and Challenges Associated with Intentional and Unintentional Use

Reviewer's code: 01548565

Position: Editorial Board

Academic degree: MD

Professional title: Director

Reviewer's country: China

Author's country: United States

Reviewer chosen by: Ruo-Yu Ma

Reviewer accepted review: 2019-10-30 12:34

Reviewer performed review: 2019-10-30 12:55

Review time: 1 Hour

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

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Drug induced liver injury (DILI) is a common cause of acute liver injury. Hepatotoxicity from paracetamol overdose is the most common cause of DILI worldwide. Paracetamol remains a significant cause of acute hepatotoxicity, as evidenced by its contribution to over half of all acute liver failure cases in the United States. This is especially concerning given that, when co-ingested with other medications. In this review, the author describe the clinical and pathophysiologic features of hepatotoxicity secondary to paracetamol and provide an update on current available knowledge and treatment options. As the results, the e conclusion is Accept (General priority).

Thank you for your kind and thought-provoking comments.

INITIAL REVIEW OF THE MANUSCRIPT

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