Author’s response to reviews

Title: Parenteral Nutrition-Drug Interactions; Antiepileptic Drugs

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Author’s response to reviews: see over
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Nehme Gabriel

Editor-in-Chief, Nutrition Journal

Revision of Manuscript: MS: 1814525838401320 - Parenteral Nutrition-Drug Interactions; Antiepileptic Drugs

First of all, I would like to express my great thanks for the constructive comments of the two anonymous reviewers on the above manuscript. We have very much appreciated these comments and have revised the manuscript accordingly as attached. We believe that these comments have helped us in enhancing the quality and clarity of the manuscript.

We have also included below a letter detailing our responses to the comments of the reviewers.

Based on the editors’ advice, we have incorporated all the necessary changes into the revised version of the manuscript. Changes made in our responses to the comments are yellow – highlighted in the revised manuscript.

Thank you for the time spent on this manuscript.

We are looking forward to receiving your favorable response.

Sincerely,

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Authors’ Responses to Reviewers

We are very thankful to the reviewers for such constructive comments which have significantly enhanced our manuscript previously entitled “Parenteral Nutrition-Drug Interactions; Antiepileptic Drugs” and now entitled “Selected Pharmacokinetic Issues of the use of Antiepileptic Drugs and Parenteral Nutrition in Critically Ill Patients”

We are pleased to inform you that we have accepted the changes you recommended or the comments you gave and we have revised the paper accordingly.

We provide the responses below detailing to each of your comments stating what changes have been made. Changes made in our responses to the comments are yellow – highlighted in the revised manuscript.

We hope the revised manuscript and this response letter have addressed the issues raised by the reviewers and would provide a satisfactory revision.

Thank you for your constructive comments and recommendations to improve this piece of work.

Sincerely,

The Corresponding Author
Detail Responses to Comments of Reviewer # 1 (S Murray)

Major Compulsory Revisions

1) I understand that this is a review paper that has looked at papers that have investigated the effects of drugs running concurrently with PN. In the abstract and the main text, the aims and objectives are not clear. There is no write up of how many studies were identified, what was the inclusion and exclusion criteria of this review and how many papers/studies were included or excluded. Furthermore there is no explanation of how the papers were synthesized in order to write up the results they did. It comes across as a paper that is potentially heavily biased and has not been produced systematically.

Authors’ response: The authors would like to thank the reviewer for this comment. They agree that this manuscript does not show the way that how conclusion was synthesized, number of studies, and inclusion & exclusion criteria. But in the meanwhile, the number of studies was not mentioned in a direct way as there was an obvious lacking of formal research evidence. So that, it will not give any sense to illustrate the number of anecdotes & case reports.

Authors’ action:

• Changes were done to the objective in the abstract and main text.
• Changes were done to the methods in the abstract and added to the main text.
• Changes were done to the conclusion in the abstract and main text.
• A new section was added “Study design” to the main text.

2) Some of the introduction is rather dated and at times incorrect.

Authors’ response: The authors are very grateful for the attention that has been paid for this manuscript. Yes, the impact of parenteral nutrition on the postoperative complication, mortality rate, and length of hospital stay has shown a great controversy with recent researches comparing to previous studies.

Authors’ action: The authors updated this issue by a meta-analysis study.

3) Some of the studies reported appear to be single case reports which may well be valid however I am weary that conclusions are being derived from these papers and presented in this paper as possible solutions to medical problems when they have not necessarily been validated correctly.

Authors’ response: The authors would express their thankful feelings to the reviewer regarding this comment. Yes, it is really an important issue to be highlighted.
Authors’ action: The authors added a new section “Critical analysis of lack of evidence” to the text just before the conclusion and amendments were also done in the conclusion in the abstract and in the main text.

**Minor Essential Revisions**

1) The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

Authors’ response: The authors are really interested to do amendments to improve the quality of this manuscript.

Authors’ action: Amendments were done.

2) In some areas of the text there is too much written about matter that is not relevant to the apparent aims of the report.

Authors’ response: The authors agree that there was too much written about matter might be not directly related to the aim of this reviews.

Authors’ action: Section 2 “Parenteral nutrition and anticonvulsants in clinical practice” was deleted in the main text.
Detail Responses to Comments of Reviewer # 2 (Jose Cavazos)

Major Compulsory Revisions

1) I would recommend the title of the article be changed since a lot of the article does not talk about TPN drug interactions and AED’s; what it does cover is a lot of protein binding issues and hypoalbuminic situations. I would suggest that the title be changed to something like- “Selected Pharmacokinetic Issues of the use of AED’s and TPN in Critically Ill Patients”.

Authors’ response: The authors show no reservation on the new title.

Authors’ action: The title of this manuscript was changed to “Selected Pharmacokinetic Issues of the use of Antiepileptic Drugs and Parenteral Nutrition in Critically Ill Patients”.

2) A review article on AED’s should also discuss newer AED’s available in IV formulation such as levetiracetam and lacosamide. I know that they have limited protein binding, but that is part of the point. However, the limited pharmacokinetic evidence for these and older AED’s should be highlighted.

Authors’ response: The authors would like to express their thanks to the reviewer for such important and significant comment.

Authors’ action: A new section “New generation antiepileptic drugs” was added to this manuscript, and some amendments were done on Table 4.

3) The authors use of anecdotes and case reports is liberal without critical analysis of lack of evidence. This is not acceptable.

Authors’ response: The authors are really happy with such constructive comment.

Authors’ action: The authors added a new section “Critical analysis of lack of evidence” to the text just before the conclusion and amendments were also done in the conclusion in the abstract and in the main text.

Minor Essential Revisions

1) Suggest that section 2 (pg 5) be deleted since does not really add anything to paper

Authors’ response: The authors agree to delete this section.
Authors’ action: Section 2 was deleted.

2) Pg 9- two typos- levetiracetam and oxcarbazepine spelled incorrectly

Authors’ response: The authors appreciate this attention.

Authors’ action: These two typos were corrected.

3) pg 11 section 3.1- why not give examples relevant to AED’s: VPA and TPN physical incompatibility; PHT and enteral feeds?

Authors’ response: The authors agree with this comment

Authors’ action: Example was added.

4) Table 4 – shouldn’t this table reflect the information on alpha glycoprotein binding of phenytoin that is discussed on pg 14 to be consistent.

Authors’ response: This Table was amended to include only antiepileptic drugs (Old & New AED), which mainly reflect the binding to albumin.

5) pg 15- I really think that the article should point out that in vivo with re equilibration it is the free fraction that changes and not free drug in regard to phenytoin and displacement-only inhibiton of metabolism of phenytoin by another drug will increase absolute free drug; given the information on ibuprofen it is not clear what happens in vivo and that should be pointed out by the authors.

Authors’ response: Yes, it was very valuable comment.

Authors’ action: Phrases were added to the text to explain the in vivo situation.

6) pg 17 third paragraph- second line should read “…follows nonlinear kinetics with…..”

Authors’ response: Authors try to revise this phrase.

Authors’ action: some amendments were done accordingly.

7) I would suggest section 7.3 be deleted completely since not relevant for the subject of the article.

Authors’ response: After a long discussion, the authors found that this section has a complementary role to the topic of this reviews.

Authors’ action: Section was not deleted.