Author's response to reviews

Title: Phenytoin versus Leviteracetam for Seizure Prophylaxis after Brain Injury - A Meta Analysis

Authors:

Syed Nabeel Zafar (zafar.nabeel@gmail.com)
Abdul Ahad Khan (ahad5@hotmail.com)
Asfar A Ghauri (asfarghauri@gmail.com)
Muhammad Shahzad Shamim (shahzad.shamim@aku.edu)

Version: 2 Date: 27 March 2012

Author's response to reviews: see over
Dear Mr Arnold Bongcayao

Thank you very much for your response and review of our manuscript titled ‘Phenytoin versus Leviteracetam for Seizure Prophylaxis after Brain Injury - A Meta Analysis’ (ref MS: 4731608567631987).

We have addressed the minor changes suggested by the editorial team and the reviewers. A point by point response to the comments is attached at the bottom of this letter. Our responses are in blue font.

Thank you very much.

Best wishes
Dr Shahzad Shamim
(On behalf of all authors)

Editorial comments

The ‘acknowledgements’ and ‘source of funding’ section has been added to the end of the manuscript. We have no one to acknowledge and have received no funding.

The manuscript conforms to the journal style and is correctly formatted.

Reviewer’s report

Title: Phenytoin versus Leviteracetam for Seizure Prophylaxis after Brain Injury - A Meta Analysis
Version: 1 Date: 19 March 2012
Reviewer: Carolyn Benson
Reviewer’s report:
Overall, good review of a topic that has not been well studied.

Thank you very much for your review and kind words.

Abstract:
In the background section, is it really fair to say that LEV is becoming the treatment of choice? It remains second line at my centre.

This sentence has been replaced by “However, a new drug Levetiracetam (LEV) is emerging as an alternate treatment choice.”

Overall:
The review would flow better if methods came before results.

This has been corrected; the methods section is now before the results section
Why was data on sex collected and presented? Have previous studies demonstrated differing efficacy in male vs female for either drug? If so, would be useful to include.

No, we have not found any data to suggest that the drug’s efficacy varies by gender. Data on sex was collected and presented to describe the characteristics of the population under investigation in each study. Differences in demographic variables like age and sex may affect the homogeneity of the meta-analysis and this should be tested for as we have done so.

In table 1, there is significant variation in drug doses for both PHY and LEV. I think there should be a comment on this in the discussion.

A comment on this has been added to the last paragraph of the discussion as a limitation.

Needs to be carefully checked for grammatical errors.

Thank you, this has been done

Discussion:

Paragraph 1, Line 3: “despite paucity of evidence in its support” – is this a fair statement? Is there not good evidence for early seizure prophylaxis in TBI?

This phrase has been removed

Paragraph 3: In paragraph 2, you state a percentage of patients that discontinue PHY due to side effects. Is there a similar statistic available for LEV?

The following sentence has been added to the discussion in the mentioned paragraph.

“Milligan et al. in their study demonstrate that 64% of patients on Levetiracetam adhered to therapy after 12 month follow up as compared to 26% of patients on Phenytoin.”

Paragraph 3: while the high cost of LEV does make its use in developing countries difficult, this problem is not limited to developing countries. Upon discharge from hospital, limited drug plans make it difficult in developed countries as well.

Thank you very much for pointing this out. The following sentence has been added to the discussion instead of the sentence about the payment being difficult in developing countries “Out of pocket payment systems in developing countries and limited discharge drug plans in developed countries make it a burden for the patient to bear this additional cost”

Paragraph 5: Could you provide more details on the variation in the early seizure time frame?

The following has been added to the discussion “Since this was an analysis of published literature we were limited by the time interval in which each study assessed seizure activity. ‘Early seizures’ varied between 3 days, 7 days, 30 days or ‘till discharge’. Even though we found no heterogeneity in the results due to this variation, it remains a limitation of the study. We were however, able to study effects for a consistent definition of ‘late seizures’ (1 month to 6 months). Even though this may not be a typical
**Reviewer's report**

**Title:** Phenytoin versus Leviteracetam for Seizure Prophylaxis after Brain Injury - A Meta Analysis  
**Version:** 1  
**Date:** 21 March 2012  
**Reviewer:** Judith Marcoux

**Reviewer's report:**

General appreciation:
1) The meta-analysis proposed by SN Zafar et al. to compare the efficacy of Phenytoin versus Leviteracetam in preventing seizures addresses a very contemporary issue in neurosurgical care. As shown in recent literature on the subject, the traditional Phenytoin is being progressively replaced by Leviteracetam for seizure prophylaxis in neurosurgical patients, without scientifically sound proof of a superior efficacy of the newer, and more expensive agent. Trying to cumulate all the available data comparing the two agents is therefore useful.
2) The literature search is exhaustive, the methodology detailed, and the analysis is overall adequate.

Thank you very much for your valuable review and kind comments

Minor essential revision:

3) In the pdf document, the methods section was after the results. This has to be corrected

This has been corrected, thank you

4) p 5 and p 8 of the manuscript: the term "early seizure" is not used in a standard definition here. Early post-traumatic seizures are defined as occurring within seven days and late after seven days. There is no such clearcut definition for other neurosurgical pathologies. The analysis of the published data renders the use of that definition difficult since many papers use different definitions. The authors choose to use a compromising solution with late seizures defined as after 1 month. This is a limitation of the meta-analysis and should be emphasized more in the discussion; or even better try to have results for seven days. The duration of therapy is of paramount importance to the occurrence of side effects.

Thank you very much for this important point. We have added the following to the mentioned paragraph.

“Since this was an analysis of published literature we were limited by the time interval in which each study assessed seizure activity. ‘Early seizures’ varied between 3 days, 7 days, 30 days or ‘till discharge’. Even though we found no heterogeneity in the results due to this variation, it remains a limitation of the study. We were however, able to study effects for a consistent definition of ‘late seizures’ (1 month to 6 months). Even though this may not be a typical definition of ‘late seizures’ it does provide us with a reliable measure to compare efficacy of the two drugs.”
5) A major point of comparison that is lacking here is the cost-effectiveness of both therapies. This point should be elaborated in the discussion.

This has been added to the discussion section

“The other potential disadvantage is the high cost of the drug, which makes its use difficult. Out of pocket payment systems in developing countries and limited discharge drug plans in developed countries make it a burden for the patient to bear this additional cost. In developed countries, limited drug plans upon discharge proves to be a hindrance for the patient to receive the medication. A recent study comparing the cost effectiveness of both drugs has estimated that for post-traumatic seizure prophylaxis, phenytoin costs $1.58 per quality adjusted life year (QALY) as compared to $20.72 per QALY for levetiracetam [6]. The authors concluded that levetiracetam can only be considered more cost-effective to phenytoin if it prevented 100% of seizures and cost < $400 for a 7 day course. However a limitation of this study is that it did not account for the costs related to monitoring of phenytoin blood levels or for the cost of side effects. The study assumed that ‘severe adverse events that could impact costs were rare for each drug’”

6) Page 7 of the manuscript, last paragraph, line 5, there is a typo: it should be "studies" and not "studied"

Thank you, this has been corrected as have other similar typos.