Author’s response to reviews

Title: Adverse drug reactions associated with six commonly used antiepileptic drugs in southern China from 2003 to 2015

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you to BMC Pharmacology and Toxicology for their policy of an open peer review. I have confirmed the names of the reviewers and their comments via the action links. We would like to express our great appreciation to Prof. Sam Salman and Balamurugan Tangiisuran, Ph.D. for their comments on our manuscript titled “Adverse drug reactions associated with six commonly used antiepileptic drugs in southern China from 2003 to 2015” (PHAT-D-18-00223). These comments were very valuable and helpful. We have carefully read the comments and made corrections that we hope meet with approval. We hope that the revised manuscript
provides more accurate and in-depth information regarding the safety of antiepileptic drugs (AEDs). All changes to the manuscript are indicated in the text using tracked changes and the line numbers of each page in the text are shown. The main modifications in the manuscript and the point-by-point responses to the reviewers’ comments are as follows:

Responses to Prof. Sam Salman:

Sam Salman (Reviewer 1): The work presents an analysis of a large number of patients and events, however, there are some key shortcomings in the current presentation of this data. These include lack of statistical testing and no descriptions or comparison between those that experienced AEs and those who did not in the registry.

There is room to improve wording to better convey the intended message in some areas.

Responses:

We agree with Prof. Sam Salman. Actually, in this study, we reviewed the data of patients who had only taken one or more of six commonly used antiepileptic drugs (AEDs), carbamazepine (CBZ), valproate (VPA), lamotrigine (LTG), oxcarbazepine (OXC), topiramate (TPM) and levetiracetam (LEV), and were registered in Wenzhou Epilepsy Follow-Up Registry Database (WEFURD) between 2003 and 2015. However, in the original manuscript, we only analyzed the 5049 adverse drug reactions (ADRs) caused by the single use or combinations of the above six specific AEDs. According to the suggestion, we compared the two groups (epilepsy outpatients with and without ADRs), and the detailed results are provided in the new Table 1 of the Tables file (Table 1, page 1). Accordingly, the abstract, methods, results and discussion sections have been modified in the revised manuscript. The modified section is located in the Abstract section, line 5 to 22, page 2; the Methods section, line 14 to 17 and line 20 to 24, page 6; the Methods section, line 1 to 19, page 7; the Methods section, line 20 to 25, page 8; the Results section, line 2 to 9 and line 14 to 19, page 10; the Discussion section, line 4 to 12, page 12.

We agree that the wording in some places was not precise. Thank you for your advice. We have revised the vague words and sentences, and the modified full text has been polished by AJE editors.

Abstract

- It should be clearly stated throughout the abstract and conclusions that the work includes only patient with epilepsy, rather than all uses of the reported medications.

Responses:
We agree with the reviewer. The study population in this study included only epileptic patients and not those using AEDs for other reasons (as AEDs are also used for migraines and neuralgia). Thank you for your suggestion. The Abstract section, line 2 to 4, line 7 and line 16 to 17, page 2 was modified.

Background

- Page 4 - Suggest re-wording the third sentence (starting with "Currently, studies …). As written it suggest that RCTs were performed to specifically study ADRs of these agents.

Responses:

We agree. The sentence (starting with "Currently, studies …) was inappropriate. The RCTs we cited were not conducted to study only the ADRs of AEDs, but to assess AED effectiveness and safety. Thank you for your suggestion. We have rewritten the sentence in (the Background section, line 6 to 9, page 4).

Methods

- Page 6 - With regards to the classification was this performed by only one of the epileptologists alone or both together. If the former then the risk of bias with different assessors should be raised. If the latter then a description on how differences in assessment between the two were adjudicated.

Responses:

We apologize for the confusion. A total of 12 doctors (two epileptologists and ten physicians) completed the assessment, which lasted nearly a year. The causality assessment of an ADR was performed independently by two physicians based on the WHO-UMC criteria, and this work was completed by eight physicians. The other two physicians checked the consistency of the assessment results. For ADRs with inconsistent assessment results, the two epileptologists re-evaluated the results together. The ADRs that remained controversial after the reassessment process were discussed by all team members. If the ADRs were still uncertain, the causality level of those ADRs was considered conditional/unclassified. Before independent evaluation, we conducted unified training and arranged for personnel to check the consistency of the results. The ambiguous ADRs were discussed together. Despite our training, verification and discussion, bias from evaluators remains unavoidable, and we have endeavored to minimize it. Thank you for your opinion. We have provided a supplementary explanation in the Methods section, line 9 to 19, page 7.
Also in reference to this assessment just to confirm that all ~5,000 ADRs were assessed by only two doctors.

Responses:

As mentioned in the above response, only ADRs with inconsistent assessment results were discussed by the two epileptologists together. The original sentence was unclear. We have made corrections and apologize for the misunderstanding. Please find the revised text in the Methods section, line 15 to 17, page 7.

Page 7 - The sum provided is not correct. 300/1000 + 1000/1500 = 0.3 +0.666… = 0.97

Responses:

We accept the reviewer's suggestion and agree that is more accurate to report to two decimal places rather than one. We have revised the text in line 17 of Page 8. Accordingly, in Supplementary Table 1 (the original table 4 of the Tables file), "Dosage/DDD", we have modified this column to two decimal places. Thank you for your advice.

Page 7 - 'n' need to be defined here

Responses:

We apologize that we did not define 'n'. In the manuscript, 'n' stands for number. We have revised the text in line 19 of Page 8.

Results

Page 8 - In reference to the last sentence is it not clear why no statistical tests were performed here, or for any other assessment in this review. This is a shame given the size of the dataset and detracts from the value of the work.

Responses:

We apologize that we had not conducted statistical analyses and that the results were not rigorous enough without testing. We thank the reviewer for this suggestion. We have performed statistical analyses in the revised manuscript. We combined the original Table 1 and Table 2 and then compared the difference in severe adverse reactions (SARs) and non-SARs using appropriate statistical tests. The new Table 2 of the Tables file provides these results. The text has also been revised in the Results section, line 14 to 19, page 10.
- Page 9 - The last sentence needs to be re-worded as it is difficult to interpret in the current form.

Responses:

We accept the suggestions of reviewer and agree that the last sentence was inappropriate. Thank you for your advice. The original sentence is unclear and the result cannot be obtained due to lack of statistical tests. We have deleted the original sentence traced in line 14 of Page 11.

Discussion

- Page 10 - The authors state "Differences in ADRs due to gender may be attributed to genetic polymorphism". This statement is false as genetic polymorphism is not related to gender. In the provided reference the same statement also is present. The original reference discusses variants in CYP enzymes influencing phenytoin severe cutaneous adverse reactions. The original reference should be provided where possible. In this case the statement needs to be changed and further consideration to the greater number of AEs in females made.

Once again no statistical testing was performed in providing this conclusion.

Responses:

We accept the opinion of Prof. Sam Salman. This sentence "Differences in ADRs due to gender may be attributed to genetic polymorphism" was incorrect. We have read the original reference titled "Genetic Variants Associated With Phenytoin-Related Severe Cutaneous Adverse Reactions". The main findings of this study was the identification of CYP2C variants, including CYP2C9*3, known to reduce drug clearance, as important genetic factors associated with phenytoin-related severe cutaneous adverse reactions. We agree that gender differences in ADR cannot be explained by genetic polymorphism. We reviewed our research data and found that the high percentage of females experiencing ADRs (53.8%) may be attributed to a greater number of ADRs in females and intolerable ADRs in females. There were approximately three ADRs (2717/893) per female and two point five (2332/914) per male. Females exhibited more SARs than non-SARs (59.4% vs. 53.1%, p = 0.006).

Thank you very much for noting this error and providing suggestions.

- Page 10 - In reference to the psychiatric vs CNS AEs it would be of great value to provide some further information on these (even a qualitative assessment) to provide the reader with greater insight and guidance.
Responses:

We thank Prof. Sam Salman for this suggestion, which could provide additional information to readers. We are willing to provide qualitative data; however, considering the word limitation of the manuscript, we only describe ADRs with a frequency greater than 5% of the psychiatric ADRs in the Discussion section, line 6 to 9, page 13.

Conclusions

- Page 13 - The authors have provided no data to support their final statement regarding omissions with SR compared to active monitoring.

Responses:

We accept this suggestion from the reviewer. The original sentence was inappropriate due to lack of supporting data. We have rewritten the sentence and provide the data from the perspective of data quality. Please find the corrected sentences in the Conclusions section, line 9 to 12, page 15).

Tables

- Tables 1 and 2 could be combined

Responses:

Thanks for your suggestion. We have combined the original Table 1 and Table 2 into a new table, which is the new Table 2. Variables of each AED and Dosage/DDD groups were added in the new Table 2, and 5049 ADRs were compared for severity and nonseverity. Please view the new table in the Tables file, Table 2, page 2 to 3.

Responses to Balamurugan Tangiisuran, Ph.D.:

Balamurugan Tangiisuran, Ph.D. (Reviewer 2): General comment:

This is a prospective observational study involving 4563 epilepsy patients. A secondary data analysis from the WEFURD registry were conducted to identify the common ADR associated with six commonly used AEDs in southern China from 2003 to 2015. Although these
information have been published previously especially among paediatrics population, the data presented from the current study are focused on the Southern China region.

In general, the manuscript is moderately written with mainly focus on describing the characteristics of ADR reported due to AEDs. However, we can consider that there is no original conclusion that could be drawn. Comparing to other analysis of ADR due to AEDS, the current study include patients from all age group and does not confined to paediatrics population.

While the authors is to be commended for their effort, there are a number of questions remaining to be clarified and are outlined below by section.

Responses:

Thank you Balamurugan Tangiisuran, Ph.D. for your comments on our work. Although there have been many studies on the ADRs of AEDs in the population of children, there are relatively few studies on the epilepsy patient population in southern China, especially with more than ten years of observation and more than 3000 cases. Patients with epilepsy have concerns about ADRs before taking medications, but information provided by the spontaneous reporting (SR) is limited. The shortcomings of SR are these: (1) the data are from the total population, including epilepsy patients and non-epilepsy patients; (2) the ADR incidence cannot be calculated accurately, because the total is unknown; (3) underreporting; and (4) poor quality of the data. Based on the above situation, our epilepsy center conducted Epilepsy Long-term Follow Up Registry Study (ELFURS) in 2003. ELFURS was a single-center, prospective, and observational study on the efficacy and safety of AEDs involving only epilepsy outpatients in southern China. In this study, we aimed at investigating the ADRs associated with six commonly used AEDs in southern Chinese outpatients with epilepsy from 2003 to 2015. We hope that our results could provide a reference to help clinicians use AEDs safely, and active surveillance might provide another method of pharmacovigilance in China. Conclusions in the original manuscript could not be drawn because the results were not tested by statistics. We have revised the manuscript according to the suggestions. The main results are that the overall ADR rate was 58.88% in 3069 epilepsy outpatients, and the rates of SARs caused by one, two and three or more AEDs were 9.9%, 10.0% and 19.6%, respectively (p < 0.001). The top three SOC categories were psychiatric disorders (1633/5049, 32.3%), neurological disorders (1222/5049, 24.2%) and gastrointestinal disorders (564/5049, 11.2%). We suggest that clinicians should pay attention to psychiatric ADRs and should be alert for SARs, especially when three or more AEDs used together. Thank you again.

Title

The title is appropriate and captures the content of the manuscript.
Responses:
We appreciate your approval; thank you very much.

Abstract

* Lack of information on the ADR identification process in the method section.

Responses:
We accept the suggestion. Thank you for your advice. We now provide information on the ADR identification process in the Abstract section, line 5 to 7 and 11 to 12, page 2.

Introduction

* Lack of information reported in regards to other studies worldwide that have reported the characteristics of ADR due to AEDs.

Responses:
Thank you for your comments. According to the suggestion, we have added the results of other studies on ADRs due to AEDs. The revised text can be found in the Background section, line 6 to 14, page 4.

Methods

* It is not clear how the identification and validation of ADRs were conducted. Was trigger tool method was utilised in the current study?

Responses:
We apologize for the confusion. ADRs in this study were prospectively collected and recorded in WEFURD at every visit. Registered patients were followed up every 1–3 months and evaluated by Dr. Zheng or Dr. Xu (me). During each follow-up, we asked registered patients if there were any adverse events (AEs), initially evaluated whether the AEs were related to drugs, and recorded the data in WEFURD. Relevant information was updated in the following visits. In this study, we evaluated the ADRs associated with six specific AEDs based on the WHO-UMC scale. We apologize for the confusion and have revised text in the Methods section, line 14 to 17 and 20 to 24, page 6; the Methods section, line 9 to 19, page 7.
How many centres were involved in the ELFURS? What action was undertaken to ensure the reliability of the identification and data being collected in each centre.

Responses:

The Epilepsy Long-term Follow Up Registry Study (ELFURS) was a single-center, prospective, and observational study involving only epilepsy outpatients in China. WEFURD was established simultaneously in 2003 and is maintained by trained two researchers. We apologize again for the confusion. We have revised the text in the Methods section, line 3, page 6.

Two epileptologists assessed the causality of the ADRs reported. Was this done prospectively in the ward or each cases were summarised using a case vignette for review.

Responses:

Thank you for your comments. This sentence “The causal relationship between ADRs and AEDs was assessed by epileptologists (Huiqin Xu and Rongyuan Zheng) based on the WHO-UMC scale” was not accurately described. The ADRs recorded in WEFURD were prospectively collected during each follow-up by Dr. Zheng or Dr. Xu (me) in epilepsy clinics. Registered population in WEFURD only consisted of outpatients who were diagnosed with epilepsy. This study reviewed these data and assessed the ADRs associated with the six commonly used AEDs based on the WHO-UMC scale. We have revised the text in the Methods section, line 14 to 17 and line 20 to 24, page 6; the Methods section, line 9 to 19, page 7.

Potential information bias - there are several studies have been published showing the existence of variability between healthcare professionals and also in the method utilised for the identification of ADRs. What was done if there was discrepancy between the reviewers during the classification process?

Responses:

Thank you for your comment. Before assessment was performed based on the WHO-UMC scale, we conducted unified training for 12 researchers (two epileptologists and ten physicians). Each ADR was independently evaluated by two physicians, and the results were verified. The ADRs with inconsistent results were discussed by two epileptologists together. Those still not in agreement were discussed by the entire team. We acknowledge the subjective bias of the evaluators in this study, but we have taken measures (training, verification, discussion) to minimize bias.
Results

* It was reported that only less than 2 percent of the ADR occurred in children in the current study although they are the major group of patients using multiple antiepileptic agents. It will be interesting to know the breakdown of age based on various categories.

Responses:

We accept the reviewer’s suggestions. We also wondered whether ADRs occurred differently in different age groups. In the new Table 1 of the Tables file, we grouped the information by age; however, there were no significant differences between age groups. We now describe these results in the Results section, line 6 to 7, page 10.

Discussion

* Page 10; Line 7: The systematic process mentioned was not detailed in the method section.

Responses:

Thank you for your suggestion. The systematic process was referred to in “the data of the 5049 ADRs were categorized with respect to age, sex, number of AEDs related to ADRs, medications, seriousness of ADRs, level of causality in the WHO-UMC scale [12] and system organ class (SOC) of the WHO Adverse Reactions Terminology (WHOART) [13], with one ADR as a unit”. We have modified the sentence because the description was ambiguous. Please find the revised text in the Discussions section, line 7, page 12).

Thanks again to all of the editors and reviewers.

Yours sincerely,

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