Author’s response to reviews

Title: Effects of valproic acid on skeletal metabolism in children with epilepsy: a systematic evaluation and meta-analysis based on 14 studies

Authors:

Li Min (limin556688@aliyun.com)
Wang Chunyan (asimipy@sina.com)
Rong Biaoxue (research568rbx@yeah.net)

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Author’s response to reviews:

BPED-D-19-00413R1
TI: “Effects of valproic acid on skeletal metabolism in children with epilepsy: a systematic evaluation and meta-analysis based on 14 studies.”

Dear Dr.:

Our manuscript has been carefully revised according to the reviewers’ suggestions and also revised according to the preferred format for the journal. The manuscript has been professionally edited for English language readability prior to resubmission to the journal. We have taken all of the comments of the two reviewers into account and wish to respond as follows:

Part A: COMMENTS OF REVIEWER #1

We sincerely thank the reviewers for their selfless help. They put a lot of effort into our manuscript, which not only involves the scientific nature of the manuscript, but also the grammatical errors of the text and the spelling of the words. We highly respect the noble quality and scientific literacy of reviewers. With their help, our work can be further improved.

I would suggest removing "in the treatment of children with epilepsy" in the first line in the abstract background section for clarity and tightening of the paragraph. Answer: We have removed this unnecessary statement.

In the second sentence of the same paragraph, the word reveal is not quite right, its a bit awkward. Instead, delineate, determine, or even evaluate would be better Answer: We have made changes based on Reviewer's suggestion. The change is showed on page 2, line 3, highlighted in blue.

In the background section of the main body of the paper, i would remove "very" from the sentence "epilepsy is a very common neurologic disease..." Answer: We have removed this word "very" from the sentence.
This entire first paragraph can be condensed to reflect the same ideas but with better flow; the sentence that starts with "long term use..." and the next sentence could be combined as "Valproic acid has been widely used as a long term anti epileptic medication"
Answer: We compressed this sentence based on the reviewers' comments, and we said: "Valproic acid has been widely used as a long term anti epileptic medication [2], it displays a certain effects in absence seizures, clinical depression, tonic-clonic seizures, juvenile myoclonic epilepsy and complex partial seizures [3, 4]", which is showed on page 3, line 1-3, highlighted in blue.

In the second paragraph in the background section, eliminate "...which is the material basis of children's height", not needed and does not add anything of value
Answer: We have eliminated the part of the sentence based on the reviewers' comments.

The next sentence " As early as...." has tense problems, should read something more like" As early as 2004, it was reported that several factors affect bone metabolism....suggesting that long term use...."
Answer: We revised this sentence based on the reviewers' comments, and we said: " As early as 2004, it was reported that several factors affect bone metabolism in children with epilepsy, suggesting that long-term use of AEDs may cause damage to the skeletal system [5]", which is showed on page 3, line 5-7, highlighted in blue.

Further on in this paragraph, there is a redundant statement; eliminate " Valproic acid is one of the commonly used drugs..."
Answer: We have eliminated the part of the sentence based on the reviewers' comments.

The next sentence "Some studies.....effect of this drug on children's metabolism" is not helpful. How many studies? there could be a short summary statement of the highlights of the studies
Answer: We revised this sentence based on the reviewers' comments, and we said, " Opinions suggest that long-term use of this drug may have an impact on bone metabolism in children [1-3, 7]", which is showed on page 3, line 9-10, highlighted in blue.

Last sentence, the word disclose is awkward: determine, or evaluate would be better
Answer: We have made changes based on Reviewer's suggestion. The change is showed on page 3, line 11, highlighted in blue.

In the methods section, the very first sentence is also awkward, "the scientific databases used in our search included" or something similar would be more clear
Answer: We revised this sentence based on the reviewers' comments, and we said: "Several databases including PubMed, Embase, Ovid, Cochrance Library, Springer Link and Web of Science were searched", which is showed on page 3, line 16-17, highlighted in blue.

Further along in that section of methods, (top of page 4) The sentence "The search strategy was defined...." is not totally clear, open to some interpretation
Answer: We explained our search strategy in depth based on the reviewers' comments, and we said: "The search strategy was to combine the topic of valproic acid with the topic of children epilepsy and to combine them with the indexes of bone metabolism. We applied boolean operators, wildcards, and field identifiers to combine search terms", which is showed on page 3, line 19-21, highlighted in blue.

In the next sentence, " this meta analysis was conducted....." instead consider "."...using the
Preferred...the use of according to is awkward
Answer: We revised this sentence based on the reviewers' comments, and we said: "This meta-analysis was conducted based on the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8]", which is showed on page 3, line 21-23, highlighted in blue.

In the inclusion and exclusion criteria paragraphs, the opening statements are not quite complete, "The inclusion/exclusion criteria used were:")
Answer: We have made changes based on Reviewer's suggestion. The change is showed on page 4, line 3 and 13, highlighted in blue.

In the inclusion criteria, number 4, can remove the "at least" at the end as you already state "more than"
Answer: We have removed the part of the sentence based on the reviewers' comments.

That same sentence should also have "The" at the beginning
Answer: We have made changes based on Reviewer's suggestion. The change is showed on page 4, line 5 and 6, highlighted in blue.

In number 5 of the inclusion criteria, the wording is awkward; instead "The control group...healthy children not receiving any medications"
Answer: We revised this sentence based on the reviewers' comments, and we said: "The control group must be composed of healthy children not receiving any medications", which is showed on page 4, line 7, highlighted in blue.

In the exclusion criteria, number 1, should start with "Studies that contained..."
Answer: We have made changes based on Reviewer's suggestion. The change is showed on page 4, line 13, highlighted in blue.

In number 3 in exclusion criteria, "children with epilepsy receiving", instead of "received"
Answer: We have made changes based on Reviewer's suggestion. The change is showed on page 4, line 15, highlighted in blue.

In the 4th statement take out "are"
Answer: We have done it.

In the next paragraph under Extraction change to "The extracted data included..." for a complete sentence to start that section
Answer: We have made changes based on Reviewer's suggestion. The change is showed on page 4, line 20, highlighted in blue.

In this paragraph, number 4, blood concentrations of what?
Answer: Some studies provide blood concentrations of valproic acid, which are shown in detail in Table 2, highlighted in blue. We revised this sentence based on the reviewers' comments, and we said: "The duration and average blood concentration of valproic acid", which is showed on page 4, line 22, highlighted in blue.

In the last one, number 5, key detection data means what? Lab values?
Answer: key detection data means bone metabolism indicators. We have modified this incomprehensible expression, we said: "Bone metabolism indicators:", which is showed on page 4, line 23, highlighted in blue.
In the next paragraph, the quality of studies "WAS" not "were", as it is the quality you are referring to
Answer: We have revised it, which is showed on page 5, line 4, highlighted in blue.

In the statistical analysis paragraph, under number 3, should say 'the meta-analysis..."
Answer: We have revised it, which is showed on page 5, line 18, highlighted in blue.

In number 5, same paragraph, the word "perform" should be in past tense, "performed"
Answer: We have revised it, which is showed on page 5, line 21, highlighted in blue.

In 7, it should be "two computer software programs"
Answer: We have revised it, which is showed on page 5, line 23, highlighted in blue.

In the Results section, the first statement instead could state "...88 did not meet inclusion criteria..."
Answer: We have revised it, which is showed on page 6, line 6, highlighted in blue.

In the next sentence, excluded is spelled incorrectly
Answer: We have revised it, which is showed on page 6, line 7, highlighted in blue.

In the second last statement in that same paragraph, note that treatment is missing the t at the end of the word, and researches should be research
Answer: We have revised it, which is showed on page 6, line 9, highlighted in blue.

Fig 1 A is referred to in this first section, however the table with the list of references included, is listed only as Table 1. Fig 1 A is the diagram of how the articles were selected
Answer: In this paragraph, we have placed the labels of Figure 1A and Table 1 in the appropriate places based on the reviewers' comments, which is showed on page 6, line 9 and 10, highlighted in blue.

In the next paragraph, "....published between 1988 and 2017" not "at" and "to"
Answer: We have revised it, which is showed on page 6, line 13, highlighted in blue.

In the same paragraph, the sentence that starts with "Boys accounted....55.5% in the control groups..."
Answer: We have revised it, which is showed on page 6, line 15 to 16, highlighted in blue.

The bold heading on this same paragraph and the next: "Included studies shows..." should be "show"
Answer: We have revised it, which is showed on page 6, line 12 and 20, highlighted in blue.

At the top of page 7, in the summary statement for that section, there should be "In" in front of the word summary
Answer: We have revised it, which is showed on page 7, line 2, highlighted in blue.

The authors have used the PRISMA and the NOS; With regards to the scoring using NOS, Figure B lists the studies and stars, and there is brief mention in the body of the paper. The reader does unfortunately either have to remember the stars and match to the references, or refer back to figure 1B. The body also states see Table 2, however that is not related to the NOS values. they only needed to refer to figure 1B at that point.
Answer: In this paragraph, we have placed the labels of Figure 1B and Table 2 in the appropriate places based on the reviewers' comments, which is showed on page 6, line 23 and page 7, line 3, highlighted in blue.
The first sentence in the vit D section of the paper, (page 8), the first sentence is confusing; that will need some clarification
Answer: We have modified this incomprehensible expression, we said: "the chi-square value was 3.12", which is showed on page 8, line 15, highlighted in blue.

The first sentence of the next page/paragraph is also confusing.... the statement is referring to heterogeneity, but there is not enough clarity in that sentence
Answer: We have modified this incomprehensible expression, we said: "The heterogeneity test on BMD of lumbar vertebrae and femur in 9 studies [7, 11-14, 17-19, 22] did not show statistical significance", which is showed on page 8, line 22 to 23, highlighted in blue.

In the paragraph "analysis of sensitivity..." the first sentence, performance is not really the right word, analysis might be better
Answer: We have revised it, which is showed on page 9, line 10, highlighted in blue.

In the discussion section, first sentence, personal disease is awkward, you mean illness or chronic disease?
Answer: Here we mean chronic disease. We have revised it, which is showed on page 9, line 20, highlighted in blue.

In the sentence starting with " as early as 2003..." The "followed by multi....." is awkward. You mean "this was followed by several multi disciplinary research studies on this topic"?
Answer: Yes, that's exactly what we mean. We have modified this incomprehensible expression using your suggestion, we said: "this was followed by several multi disciplinary research studies on this topic", which is showed on page 9, line 23, highlighted in blue.

The next sentence, remove "disorder"
Answer: We have done it.

The last sentence is very awkward, maybe instead something like "We collected observational studies on children with epilepsy receiving valproic acid to assess the potential effects of this medication on bone metabolism"
Answer: Your suggestion is quite accurate. We have modified this part with your sentence, which is showed on page 10, line 3 to 4, highlighted in blue.

The next paragraph " Our analysis included...." needs more work than I can suggest here, there are incomplete sentences, grammatical errors and will need a significant re edit to correct.
Answer: We revised this sentence based on the reviewers' comments, and we said: " A total of 14 studies [11-23] were included in our analysis. We found that the long-term use of valproic acid did not affect the levels of blood calcium, phosphorus, ALP and osteocalcin in epileptic children. Although it did not reach a statistical significance, we found that children with epilepsy taking valproic acid had relatively higher PTH levels than those who did not take the drug. One previous study shows that valproic acid stimulates the secretion of PTH, promotes bone absorption and increases bone conversion, which results in a decrease of BMD [26]", which is showed on page 10, line 5 to 10, highlighted in blue.

The next discussion paragraph first sentence, ".....lower than that of the healthy control group" instead of in the healthy control group
Answer: We have revised it, which is showed on page 10, line 11, highlighted in blue.
The next sentence is also awkward, "D3 all need to pass..." do you mean instead undergo action of hepatic 25 hydroxylase?
Answer: We revised this sentence based on the reviewers' comments, and we said: "Through the action of liver 25-hydroxylase, human exogenous and endogenous Vitamin D2 and D3 are converted into 25-OH-VitD, which requires the action of 1-α hydroxylase in the proximal tubule of the kidney to form active 1-25-OH-VitD [27]", which is showed on page 10, line 13 to 15, highlighted in blue.

In the next sentence, "previous study" should be "studies", and instead of "show an effect", consider "can be hepatotoxic"
Answer: We have revised it, which is showed on page 10, line 16 and 17, highlighted in blue.

In the paragraph on page 11 starting with the discussion on the use of DEXA, note the sentence "we found that both the vertebrae and femur...." should read instead "we found that for both the vertebrae and femur"
Answer: We have revised it, which is showed on page 10, line 23, highlighted in blue.

In the next sentence, "early stage", should be "early stages"
Answer: We have revised it, which is showed on page 11, line 3, highlighted in blue.

There is a statement "Previous study shows that children's bone development is more important than adults" this should be removed as not only grammatically incorrect but is a very non contributory statement
Answer: We have removed it.

The next 2 paragraphs(the last two of the discussion section of the paper) also have numerous grammatical errors and needs revision; starts at "The classic design...."
Answer: We revised this sentence based on the reviewers' comments, we said: "The 14 studies included in this meta-analysis were case-control studies with good homogeneity among the studies [11-23]. A NOS assessment showed that 12 studies had obtained more than seven stars. And the publication bias analysis showed that these studies were very unlikely to have publication bias. However, these studies have some shortcomings: first, the samples in most studies were relatively small; second, the methods and units of measurement used for bone metabolism indicators differed in these studies, which could lead to methodological heterogeneity; third, the relatively large number of studies from turkey, which may produce geographical bias; fourth, most studies did not focus on the correlation between the plasma concentration of valproic acid and bone metabolism indicators, nor did they compare the correlation between different medication time and bone metabolism indicators.", which is showed on page 11, line 7 to 16, highlighted in blue.

Part B: COMMENTS OF REVIEWER #2
We sincerely thank the reviewers for their selfless help. They put a lot of effort into our manuscript, which not only involves the scientific nature of the manuscript, but also the grammatical errors of the text and the spelling of the words. We highly respect the noble quality and scientific literacy of reviewers. With their help, our work can be further improved.

Abstract:
Background: remove 'children with' 2nd line
Answer: We have removed it.
Background:
Epilepsy is a common ....
4th line, use AED again
2nd paragraph: ... factors affect bone ..... 
..... hypocalcemia and increased fracture ..... 
suggest identify instead of 'disclose'
Answer: We have revised it, which is showed on page 3, line 5 to 7, and 11, highlighted in blue.

Methods:
.... were searched for studies ......
Answer: We have revised it, which is showed on page 3, line 16 to 17, highlighted in blue.

Exclusions: ... receiving other ....
Answer: We have revised it, which is showed on page 4, line 15, highlighted in blue.

Methodological:
.... was awarded
Answer: We have revised it, which is showed on page 5, line 7, highlighted in blue.

Results:
Included studies showed ... (1st 2 headers)
..... were published between ..... 
Answer: We have revised it, which is showed on page 6, line 13, highlighted in blue.

Discussion:
1st paragraph: last sentence ..... treatment for epilepsy in children ..... 
Answer: We revised this sentence based on the reviewers' comments, and we said: "We collected observational studies on children with epilepsy receiving valproic acid to assess the potential effects of this medication on bone metabolism", which is showed on page 10, line 2 to 4, highlighted in blue.

2nd: Of note, serum calcium ...... Delete 'we found that'
Answer: We have removed it.

4th: ... which implies that (rather than means)
Delete 'A previous study ...... adults' sentence
Answer: We have removed it.

5th: Analysis suggested that ..... publication bias ..... 
Answer: We revised this sentence based on the reviewers' comments, and we said: "And the publication bias analysis showed that these studies were very unlikely to have publication bias.", which is showed on page 11, line 9 to 10, highlighted in blue.

Figure legend: 3: ..... in children with epilepsy
legend 4: .... were not affected
Answer: We have revised it based on the reviewers' comments, which is showed on page 16, line 11 and 15, highlighted in blue.

Technical Comments:
1. Please include the Acknowledgements on your Declarations section.
Answer: We have done it, which is showed on page 13, line 8 and 9, highlighted in blue.

2. Please add figure legend headings.
Answer: We have done it, which is showed on page 16, highlighted in blue.

Editor Comments:
Please carefully review the written English
Answer: As suggested by this reviewer, the manuscript has been carefully revised regarding a standard writing format and grammar. Our manuscript has been polished by native English speakers.

We would like to extend thanks to all of the reviewers and to the editing staff at ‘BMC Pediatrics’ for this opportunity to resubmit a revised version of our work. We look forward to hearing from you, and, as before, please address all communications regarding this manuscript to myself as the corresponding author.

Rong Biaoxue, Department of Medicine, Shenmu Hospital, Shenmu, 719300, Yulin City, Shaanxi, China. Tel: +86 15349260656. E-mail: research568rbx@yeah.net