Reviewer’s report

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

Version: 1  Date: 13 Nov 2019

Reviewer: Barbara Blackie

Reviewer's report:

Thank you to the authors for their hard work editing this paper

Some suggested edits as there are still tense and grammatical, as well as awkward English language use:

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

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

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..."

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"

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

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...."

Further on in this paragraph, there is a redundant statement; eliminate " Valproic acid is one of the commonly used drugs..."

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

Last sentence, the word disclose is awkward: determine, or evaluate would be better

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

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 interpretaion
In the next sentence, "this meta analysis was conducted....." instead consider "...using the Preferred....the use of according to is awkward

In the inclusion and exclusion criteria paragraphs, the opening statements are not quite complete, "The inclusion/exclusion criteria used were:")

In the inclusion criteria, number 4, can remove the "at least" at the end as you already state "more than"

That same sentence should also have "The" at the beginning

In number 5 of the inclusion criteria, the wording is awkward; instead "The control group...healthy children not receiving any medications"

In the exclusion criteria, number 1, should start with "Studies that contained..."

In number 3 in exclusion criteria, "children with epilepsy receiving", instead of "received"

In the 4th statement take out "are"

In the next paragraph under Extraction change to "The extracted data included...." for a complete sentence to start that section

In this paragraph, number 4, blood concentrations of what?

In the last one, number 5, key detection data means what? Lab values?

In the next paragraph, the quality of studies "WAS" not "were", as it is the quality you are referring to

In the statistical analysis paragraph, under number 3, should say 'the meta-analysis...."

In number 5, same paragraph, the word "perform" should be in past tense, "performed"

In 7, it should be "two computer software programs"

In the Results section, the first statement instead could state "...88 did not meet inclusion criteria..."

In the next sentence, excluded is spelled incorrectly

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

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

In the next paragraph, "....published between 1988 and 2017" not "at" and "to"

In the same paragraph, the sentence that starts with "Boys accounted....55.5% in the control groups..."

The bold heading on this same paragraph and the next: "Included studies shows..." should be "show"
At the top of page 7, in the summary statement for that section, there should be "In" in front of the word summary.

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.

The first sentence in the vit D section of the paper, (page 8), the first sentence is confusing; that will need some clarification.

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.

In the paragraph "analysis of sensitivity..." the first sentence, performance is not really the right word, analysis might be better.

In the discussion section, first sentence, personal disease is awkward, you mean illness or chronic disease?

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"?

The next sentence, remove "disorder"

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"

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.

The next discussion paragraph first sentence, ".....lower than that of the healthy control group" instead of in the healthy control group.

The next sentence is also awkward, "....D3 all need to pass..." do you mean instead undergo action of hepatic 25 hydroxylase?

In the next sentence, "previous study" should be "studies", and instead of "show an effect", consider "can be hepatotoxic"

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"

In the next sentence, "early stage", should be "early stages"
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

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...."

Overall comments;

The study has value and merit, and clearly has involved a lot of time and effort, but will still need more attention to detail and to wording, grammar and language.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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