Reviewer's report

Title: The Impact of The Use of Antiepileptic Drugs on the Growth of Children

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Reviewer: Brian D Moseley

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Major Compulsory Revisions

The article by Herng-Sheng Lee et al. details a study of growth in children taking certain AEDs. These include VPA, OXA, TPM, and LTG. The authors demonstrate that treatment with VPA was associated with significantly lower stature one year later versus controls. There was no significant difference in the serum calcium levels between these two groups, suggesting the reason for the lower stature may have been a direct effect of VPA on the proliferation of growth plate chondrocytes. This was demonstrated in 6 independent experiments looking at cell growth of growth plate chondrocytes in vitro.

I have the following major concerns with the article:

1. The sample sizes utilized in the present study are quite small. Although statistical significance was reached with regards to lower stature and VPA, it was not with OXA (n=30), TPM (n=19), and LTG (n was only 8). It is quite possible that statistically significant lower statures would have been discovered after one year in children taking some or all of these AEDs if larger sample sizes had been used. The present study is likely not powered to detect small changes in stature with AED use that would be expected after only one year of AED use. If the authors do not have additional data from more subjects to add to a subsequent revision, this major limitation needs to be admitted in greater detail in the discussion section (only a portion of one sentence is spent addressing it).

2. Why was the decision reached to look at serum calcium levels rather than or in addition to serum vitamin D levels? As the authors point out, enzyme inducing AEDs have been shown to increase the catabolism of vitamin D to inactive metabolites, potentially explaining why some enzyme inducing AEDs are associated with increased risk of osteoporosis. This limitation needs to be addressed in the discussion section.

3. How was the decision reached to select the specific AEDs used in the present study? Was it randomized? If not, this introduces bias and needs to be addressed in the discussion section.

4. The fact that the authors only followed children for one year may have not permitted detection of more subtle abnormalities in growth. This should be admitted as a limitation in the discussion section.

5. More information about the specific serum calcium values for the control subjects should be included (e.g. have controls be part of Figure 2).
6. In the conclusions section, the authors state that prevention of growth retardation and adverse bone health with the use of VPA can be addressed by judicious use of AED therapy coupled with improved nutrition and promotion of weight bearing activities. The present study does not address the later interventions. Therefore this statement needs to be softened with the use of the word “may” rather than “can.”

Minor Essential Revisions

In the background section, epilepsy is described as involving “epileptic crises.” This is a bizarre phrase and should be changed to “epileptic seizures.” In addition, it is possible to diagnose epilepsy after only one epileptic seizure if an “endearing predisposition of the brain to future seizures” exists (as discovered on further testing such as MRI brain and EEG).

Discretionary Revisions

The authors use an older system of classification to describe the types of epilepsy (idiopathic generalized epilepsy) that they examined in the present study. A newer classification system exists (see Berg et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010 Apr;51(4):676-85.). The authors should really consider adjusting their language to fit with the new classification scheme, as this is the preferred classification system for research.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.