



## Correspondence

## Comparative Effectiveness of Phenobarbital versus Levetiracetam for Infantile Epilepsy



To the Editor,

We read with great interest a summary of our recent work comparing levetiracetam to phenobarbital in infants.<sup>1,2</sup> We were honored to see the article flagged for the readership. However, the commentary misrepresents aspects of our work, which we would like to correct.

First, the Early Life Epilepsy Study was not a retrospective chart review. Rather, it was a prospective observational study of infants and toddlers with newly diagnosed epilepsy. We obtained consent from every enrolled patient, allowing us to contact the family in instances where there were missing or ambiguous data. Furthermore, we enrolled the patients before ascertainment of their outcomes, mitigating bias.

Second, our outcome was not “on monotherapy,” but rather a combined outcome of “freedom from failure of monotherapy.” To meet this outcome, an infant had to be on monotherapy with the initial medication (or no treatment) *and* seizure free for three months.

Third, we mitigated several known biases associated with observational comparative effectiveness research. We controlled for observed selection bias using propensity score techniques; we controlled for within-center correlations using generalized estimating equations; and we managed missing data with multiple imputation.

Fourth, the effect size was large. Our final estimate indicated that levetiracetam was superior to phenobarbital with an odds ratio of 4.2 (95% confidence interval: 1.1 to 16) and a number needed to treat of 3.5 (1.7 to 60). Large effect sizes require large biases to produce if spurious.

Fifth, we performed a sensitivity analysis to address the concern that “phenobarbital may have been more commonly used in children who worried the clinician.” We repeated the main analysis excluding early failures (i.e., children who required a second anti-seizure medication within one week of starting the first). We reasoned that early failure might indicate difficult-to-treat epilepsy, which could be correlated with factors not captured in our data. This analysis strengthened confidence in our findings. The odds ratio in favor of levetiracetam increased from 4.2 (1.1 to 16) in the main analysis to 4.8 (1.3 to 18) in the sensitivity analysis.

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We are grateful that our work was highlighted in *Pediatric Neurology*. We agree that it may be difficult to conduct a randomized controlled trial to test our results. In the absence of such a trial, this rigorous study with robust statistical methods provides confidence in our conclusion: for infants with new-onset epilepsy, an initial trial of levetiracetam is more likely to result in freedom from failure than phenobarbital.

## References

1. Pavlakis SG. Short Takes. *Pediatr Neurol*. 2018;89:1–2.
2. Grinspan ZM, Shellhaas RA, Coryell J, et al. Comparative Effectiveness of Levetiracetam vs Phenobarbital for Infantile Epilepsy. *JAMA Pediatr*. 2018;172:352–360.

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## Reply to Grinspan et al.



I thank Grinspan et al. for elucidating the techniques in their study.<sup>1</sup> Their study was well done and likely meaningful, but that is not the point. In a 2017 article, treatment patterns for early-life epilepsy in 17 pediatric epilepsy centers were evaluated for initial therapy.<sup>2</sup> The authors of this earlier study (which included the authors in this letter) found that treatment with levetiracetam was the most commonly prescribed medication regardless of epilepsy presentation. This article concluded that, without any specific effort, the pediatric epilepsy community was consistent in the

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