



# Medications for Early Life Epilepsy: Evidence Versus Experience?

Epilepsy Currents  
2019, Vol. 19(1) 33-35  
© The Author(s) 2019  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/1535759718822130  
journals.sagepub.com/home/epi



## Comparative Effectiveness of Levetiracetam vs Phenobarbital for Infantile Epilepsy

Grinspan ZM, Shellhaas RA, Coryell J, Sullivan JE, Wirrell EC, Mytinger JR, Gaillard WD, Kossoff EH, Valencia I, Knupp KG, Wusthoff C, Keator C, Ryan N, Loddenkemper T, Chu CJ, Novotny EJ Jr, Millichap J, Berg AT. *JAMA Pediatr.* 2018 Apr 1;172(4):352-360. doi: 10.1001/jamapediatrics.2017.5211.

**Importance:** More than half of infants with new-onset epilepsy have electroencephalographic and clinical features that do not conform to known electroclinical syndromes (ie, nonsyndromic epilepsy). Levetiracetam and phenobarbital are the most commonly prescribed medications for epilepsy in infants, but their comparative effectiveness is unknown. **Objective:** To compare the effectiveness of levetiracetam versus phenobarbital for nonsyndromic infantile epilepsy. **Design, Setting, and Participants:** The Early Life Epilepsy Study—a prospective, multicenter, observational cohort study conducted from March 1, 2012, to April 30, 2015, in 17 US medical centers—enrolled infants with nonsyndromic epilepsy and a first afebrile seizure between 1 month and 1 year of age. **Exposures:** Use of levetiracetam or phenobarbital as initial monotherapy within 1 year of the first seizure. **Main Outcomes and Measures:** The binary outcome was freedom from monotherapy failure at 6 months, defined as no second prescribed antiepileptic medication and freedom from seizures beginning within 3 months of initiation of treatment. Outcomes were adjusted for demographics, epilepsy characteristics, and neurologic history, as well as for observable selection bias using propensity score weighting and for within-center correlation using generalized estimating equations. **Results:** Of the 155 infants in the study (81 girls and 74 boys; median age, 4.7 months [interquartile range, 3.0-7.1 months]), those treated with levetiracetam ( $n = 117$ ) were older at the time of the first seizure than those treated with phenobarbital ( $n = 38$ ; median age, 5.2 months [interquartile range, 3.5-8.2 months] vs 3.0 months [interquartile range, 2.0-4.4 months];  $P < .001$ ). There were no other significant bivariate differences. Infants treated with levetiracetam were free from monotherapy failure more often than those treated with phenobarbital (47 [40.2%] vs 6 [15.8%];  $P = .01$ ). The superiority of levetiracetam over phenobarbital persisted after adjusting for covariates, observable selection bias, and within-center correlation (odds ratio, 4.2; 95% confidence interval [CI], 1.1-16; number needed to treat, 3.5 [95% CI, 1.7-60]). **Conclusions and Relevance:** Levetiracetam may have superior effectiveness compared to phenobarbital for initial monotherapy of nonsyndromic epilepsy in infants. If 100 infants who received phenobarbital were instead treated with levetiracetam, 44 would be free from monotherapy failure instead of 16 by the estimates in this study. Randomized clinical trials are necessary to confirm these findings.

## Commentary

Phenobarbital is a broad-spectrum anti-seizure medication that was initially synthesized more than 100 years ago.<sup>1</sup> It is the oldest anti-seizure medication we regularly use to treat patients with epilepsy, and it is frequently used to treat neonates and infants. Over the last decade, phenobarbital has been used in 96% of neonates with seizures, typically as a first-line agent.<sup>2</sup> However, concerns have been raised about poorer cognitive outcomes with the use of phenobarbital. For example, Maitre et al found worse neurodevelopmental outcomes in neonates with increased exposure to phenobarbital but not levetiracetam.<sup>3</sup>

With additional anti-seizure medications available, newer options are now considered first-line treatment for infants with epilepsy. Levetiracetam is approved as adjunctive therapy for focal seizures in children as young as 1 month of age and generalized seizures for children age 6 years and older. It is used off label as monotherapy or adjunctive therapy for focal and generalized seizures, as well as status epilepticus, in all ages, including neonates.<sup>4</sup> In North America, levetiracetam is the preferred treatment for focal seizures in infants, and globally, it is one of the first-line treatments for generalized and myoclonic seizures. Phenobarbital is a first-line treatment for generalized seizures.<sup>5</sup> A prospective multicenter study of



Creative Commons Non Commercial No Derivs CC BY-NC-ND: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>) which permits non-commercial use, reproduction and distribution of the work as published without adaptation or alteration, without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).



children diagnosed with epilepsy before age 36 months demonstrated nearly 2/3 of nonsyndromic children were treated with levetiracetam as first choice, followed by oxcarbazepine, phenobarbital, topiramate, and zonisamide. However, 31% of infants under age 6 months were treated with phenobarbital.<sup>6</sup>

In the current era of rapidly expanding lists of anti-seizure medications, how do we know which ones are best to use in one of our most vulnerable populations? The continued use of phenobarbital is likely due to lack of good evidence to support the use of other medications. Currently, no anti-seizure medications have been approved by Food and Drug Administration (FDA) for use in neonates and few are approved for infants.<sup>2</sup> Most clinical trials of anti-seizure medications exclude children of any age, especially infants.<sup>7</sup> Once a medication is approved for adults, approval in pediatrics may take an average of 8 additional years. In the meantime, medications are used off label, which may increase the risk of adverse medication reactions.<sup>8</sup> The International League Against Epilepsy (ILAE) Commission of Pediatrics carefully reviewed the current information available for treatment of seizures beginning in infancy and found strong evidence that levetiracetam is effective for the treatment of focal seizures in infants. However, the evidence for the preferred treatment of generalized seizures, benign infantile convulsions, benign myoclonic epilepsy of infancy, and provoked/situational seizures was weak, resulting in an overall lack of evidence-based recommendations for this population.<sup>9</sup>

Without evidence, we fall back on the next best option for decision-making: experience. However, “because that’s what we’ve always done” is not a replacement for practicing evidence-based medicine. The answer to this initially seems simple—do more studies of efficacy and safety of anti-seizure medications in neonates, infants, and children. Obtain the evidence-based information. However, this view may be overly simplistic and fraught with challenges.

The pediatric population is a vulnerable population, especially neonates and infants, making rigorous consent and safety monitoring of utmost importance. Parents fear anti-seizure medication side effects, with up to 86% reporting an adverse drug event in their child.<sup>10</sup> Consequently, parents may fear enrolling their child in drug studies. This is also a population of great variability in size (comparing a neonate to a child) and metabolism, making pharmacokinetics challenging. In addition, when pediatric trials for drug development are created, there is a high trial failure rate due to difficulties with dose selection and trial design.<sup>8</sup> Finally, infant-onset epilepsy is rare, making recruitment challenging.

The Pediatric Epilepsy Research Consortium (PERC) is attempting to face this apparently insurmountable list of challenges. Pediatric Epilepsy Research Consortium is a network of approximately 40 US pediatric epilepsy academic centers that have come together to facilitate collaborative practice-changing research to improve the care of children with epilepsy. Recognizing that many pediatric epilepsy syndromes are rare, this network of centers allows research to occur on a larger

scale than previously possible. The Early Life Epilepsy Study (ELES), highlighted in this commentary, is a prospective observational cohort of children with epilepsy onset before age 3 years that comprises 17 US pediatric epilepsy centers, all of whom are members of PERC.

Over the course of 3 years, children with epilepsy onset prior to age 3 years were prospectively enrolled in the ELES and information regarding seizure type, syndrome, and medications were recorded. Physicians were allowed to prescribe according to his or her preference and were not given specific guidance regarding which medications to use. Through this database, the ELES identified 243 children with nonsyndromic epilepsy beginning between age 1 month and 1 year of age. Although 88 infants were ultimately excluded, this remains the largest cohort of prospectively followed infants with nonsyndromic epilepsy. Prescribing practices in this study reflect the ILAE recommendations, with the majority of children (117) receiving levetiracetam and a minority (38) receiving phenobarbital. Furthermore, those that received phenobarbital were, on average, 2 months younger than those who received levetiracetam, consistent with previous prescribing practices. Fortunately, the size of this study allowed for weighting for observable selection bias. Overall, levetiracetam was found to be significantly more effective as initial monotherapy for infants with nonsyndromic epilepsy.

Given the significant feasibility challenges of conducting a gold standard randomized, placebo controlled, blinded study in infants and neonates, carefully designed observational studies such as the one highlighted here provide excellent evidence-based information that clinicians can use in practice when treating infants with epilepsy. This study is consistent with, and supportive of, the current practice of using levetiracetam preferentially over phenobarbital. Hopefully, studies such as this one will ultimately lead to changes in FDA approval. Furthermore, and perhaps of greater importance for future practice, this study provides a method to examine efficacy of treatment options for this unique population.

*By Katherine Nickels*

## References

1. Kwan P, Brodie MJ. Phenobarbital for the treatment of epilepsy in the 21st century: a critical review. *Epilepsia*. 2004;45(9):1141-1149.
2. El-Dib M, Soul JS. The use of phenobarbital and other anti-seizure drugs in newborns. *Semin Fetal Neonatal Med*. 2017;22(5):321-327.
3. Maitre NL, Smolinsky C, Slaughter JC, Start AR. Adverse neurodevelopmental outcomes after exposure to phenobarbital and levetiracetam for the treatment of neonatal seizures. *J Perinatol*. 2013;33(11):841-846.
4. Micromedex<sup>®</sup> (electronic version). IBM Watson health, Greenwood Village, Colorado, USA. <https://www.micromedexsolutions.com/> (cited: 11/16/2018).



5. Wilmshurst JM, Burman R, Gaillard WD, Cross JH. Treatment of infants with epilepsy: common practices around the world. *Epilepsia*. 2015;56(7):1033-1046.
6. Shellhaas RA, Berg AT, Grinspan ZM, et al. Initial treatment for nonsyndromic early-life epilepsy: an unexpected consensus. *Pediatr Neurol*. 2017;75:73-79.
7. Arzimanoglou A, Losch C, Garate P, Bentz J. Safety of levetiracetam among infants younger than 12 months—results from a European multicenter observational study. *Eur J Paediatr Neurol*. 2016;20(3):368-375.
8. Mehrotra N, Bhattaram A, Earp JC, et al. Role on quantitative clinical pharmacology in pediatric approval and labeling. *Drug Metab Dispos*. 2016;44(7):924-933.
9. Wilmshurst JM, Gaillard WD, , Vinayan KPI, et al. Summary of recommendations for the management of infantile seizures: task force report for the ILAE commission of pediatrics. *Epilepsia*. 2015;56(8):1185-1197.
10. Bach VA, Neining MP, Spindler UP, et al. How do parents perceive adverse drug events of their children's anticonvulsant medication? *Eur J Paediatr Neurol*. 2018;22(3):427-433.