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Comparative Effectiveness of Levetiracetam vs Phenobarbital for Infantile Epilepsy

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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 vs 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% CI, 1.1-16; number needed to treat, 3.5 [95% CI, 1.7-60]).

CONCLUSIONS AND RELEVANCE Levetiracetam may have superior effectiveness compared with 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.

Supplemental content

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One in 1000 infants aged 1 month to 1 year develops epilepsy,[1] suggesting that there are 130 000 new cases of infantile epilepsy per year worldwide. However, guidance on treatment of infantile epilepsy is limited.[2] High-quality, evidence-based recommendations for infantile epilepsy exist exclusively for West syndrome.[2,3] For other syndromes, such as Dravet syndrome, evidence is limited to case series and expert opinion.[4] Furthermore, more than half of infants with epilepsy have nonsyndromic presentations; that is, the clinical and electroencephalographic characteristics do not conform to recognized patterns.[5] Although there is guidance on which medications may be effective for nonsyndromic epilepsy, there is insufficient evidence to recommend one medication rather than another.[2]

Phenobarbital and levetiracetam are commonly prescribed for infants with epilepsy.[6,7] Phenobarbital, a barbiturate, has been used for epilepsy since the 1910s[8] and remains first-line treatment for neonatal seizures.[9] However, phenobarbital is associated with poorer cognitive outcomes in otherwise healthy children with febrile seizures compared with placebo.[10] Levetiracetam was approved in the United States in 1999. Its exact mechanism of action is unknown, but levetiracetam may modulate neurotransmission via synaptic vesicle protein 2A.[11] Compelling data support the use of levetiracetam in infantile epilepsy.[12] A randomized clinical trial of children aged 1 month to 4 years with refractory focal-onset seizures found that adding levetiracetam to an existing antiepileptic seizure drug (AED) regimen improved seizure control better than placebo.[13] The comparative effectiveness of levetiracetam and phenobarbital for nonsyndromic infantile epilepsy is unknown.

When 2 medications can be used for a given indication, their effectiveness can be compared using observational data.[14] We compared the effectiveness of phenobarbital vs levetiracetam using data from the Early Life Epilepsy Study (ELES).[5]

Key Points

Question Is there a difference in effectiveness between levetiracetam and phenobarbital, the 2 most commonly prescribed medications for nonsyndromic epilepsy in infants?

Finding In this multicenter cohort study of 155 infants with nonsyndromic epilepsy, freedom from monotherapy failure at 6 months was significantly more common for children treated with levetiracetam (40.2%) than those treated with with phenobarbital (15.8%). The observed superiority of levetiracetam compared with phenobarbital persisted after controlling for covariates, observable selection bias, and correlation of outcomes within centers.

Meaning These findings provide novel evidence to favor levetiracetam instead of phenobarbital for initial monotherapy of infantile nonsyndromic epilepsy, although randomized clinical trials are needed to confirm the results.

Methods

Study Design

The ELES is a prospective, multicenter, observational cohort study of children with epilepsy that began in the first 3 years of life, conducted primarily through review of medical records. The institutional review board at each of the following institutions approved the study: Ann & Robert H. Lurie Children's Hospital of Chicago, Weill Cornell Medicine, University of Michigan, Oregon Health & Sciences University, University of California San Francisco, Mayo Clinic, Nationwide Children's Hospital, Children's National Health System, Johns Hopkins Hospital, St. Christopher's Hospital for Children, Children's Hospital Colorado, Stanford University, Cook Children's Healthcare System, Children's Hospital of Philadelphia, Boston Children's Hospital, Massachussetts General Hospital, and Seattle Children's Hospital. Written informed consent was obtained from a parent or guardian for each enrolled child.

Data Sources

From March 1, 2012, through April 30, 2015, a total of 17 US pediatric epilepsy centers prospectively enrolled children. All centers were members of the Pediatric Epilepsy Research Consortium. Consistent with recent recommendations, epilepsy was defined as 2 or more unprovoked seizures occurring on different days or a single seizure if the risk of recurrence was high enough to initiate treatment.[15] Additional details are provided elsewhere.[5]

All data were collected via review of medical records and entered into a Research Electronic Data Capture database (REDCap Consortium). Site investigators (all pediatric epilepsy specialists: Z.M.G., R.A.S., J.C., J.E.S., E.C.W., J.R.M., W.D.G., E.H.K., I.V., K.G.K., C.W., C.K., N.R., T.L., C.J.C., E.J.N., and J.M.) supervised data collection. Each case was rereviewed centrally by the ELES principal investigator (A.T.B.). Inconsistencies and missing data were iteratively reviewed with site investigators until satisfactory resolution of all questions.

Exposure

The exposure was the first AED prescribed as monotherapy by a child neurologist. We excluded AEDs prescribed in the emergency department if they were discontinued at the initial neurology visit and a different medication was initiated. The target dose of the medication was recorded as free text and was not entered consistently for all patients. The ELES database did not include details of titration schedules or serum levels.

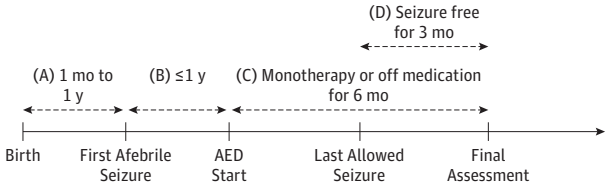
Outcome

An infant was considered to be free from monotherapy failure at 6 months if no second AED was prescribed and the infant was free of seizures beginning within 3 months of treatment initiation (**Figure 1**). This outcome allowed a 3-month titration period during which families and physicians could adjust the AED dose in case of early recurrence of seizures. A child who stopped taking the initial medication prior to 6 months but remained seizure free and without another AED was considered free from monotherapy failure. We did not consider vitamin B_6 (pyridoxine) a second medication.

Inclusion and Exclusion Criteria

We analyzed a subset of the ELES participants who had nonsyndromic epilepsy and were aged 1 month to 1 year at the time

Figure 1. Timeline for Inclusion Criteria and Definition of Freedom From Failure of Monotherapy



To be included in the analysis, a child needed to be aged 1 month to 1 year at the time of the first afebrile seizure (A) and have started an antiepileptic seizure drug (AED) within 1 year of the first afebrile seizure (B). The child was free from failure of monotherapy if no second AED was begun for 6 months (C) and there were no seizures for 3 months after 3 months of therapy (D).

of the first afebrile seizure. An infant was considered to have nonsyndromic epilepsy if the treating pediatric neurologist determined the history was not consistent with electroclinical features of an infantile epilepsy syndrome. We excluded children who were not treated with an AED during the year after the initial diagnosis of epilepsy, began AED polytherapy on the first day of treatment, started an AED while awaiting surgery for a brain tumor, were unavailable for follow-up or died prior to 6 months, or had insufficient information in the ELES database to determine if a seizure had occurred in the period between 3 and 6 months after treatment initiation.

Covariates

Demographic covariates included age at first afebrile seizure, sex, ethnicity, race, gestational age at birth (premature vs term), distance from the infant's home to the medical center (same city, ≤160 km [≤100 miles], or >160 km [>100 miles]), and insurance (public, private, or other or unknown). Clinical covariates included epilepsy etiology (structural brain malformation, neurocutaneous syndrome, acquired, genetic, other, or unknown), days from first seizure to AED, and seizure presentation (focal, generalized, or mixed or unclear). We also included the following 3 additional covariates from the neurologic history: head size (normal, microcephaly [<third percentile], macrocephaly [>95th percentile], or unknown), developmental delay (definite, mild, normal, or unknown), and brain imaging (normal, equivocal, abnormal, or not done). Clinical factors (ie, etiology, seizure presentation, and development) were determined by the treating child neurologist.

Statistical Analysis

We performed statistical analyses with SAS (SAS Institute, Inc) and R, version 3.0.2 (R Foundation for Statistical Computing). The χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables were used for bivariate analysis. $P < .05$ (2-sided) was considered significant.

We performed 4 multivariable analyses to determine the association between medication selection and the outcome under different statistical assumptions. In all 4 analyses, we adjusted SEs for the correlation of outcomes within each center using generalized estimating equations.

First, we performed an unadjusted analysis (generalized estimating equations only). Second, we created a multivariable model that adjusted for covariates that were statistically different in the bivariate analyses with a significance of $P < .10$. This model accounted for variables known to be important from the bivariate analysis while minimizing statistical noise introduced by variables not clearly associated with medication selection.

In the third and fourth analyses, we accounted for selection bias among observed characteristics with an inverse probability of treatment weighting[14] technique called *weighting by odds*[16] (also called *standardized mortality ratio weighting*[17] or *average treatment effect on the treated*[14]). Inverse probability of treatment weighting mirrors the counterfactual logic of a matched pair analysis but incorporates data from the entire cohort.[14] We used inverse probability of treatment weighting to estimate the effect of changing treatment to levetiracetam among infants who received phenobarbital. To do so, we developed a propensity score (PS) using logistic regression to estimate the probability that an infant would receive phenobarbital. We included all covariates in the PS. We assigned a weight of 1.0 to individuals treated with phenobarbital and used the PS to weight the others by the odds of treatment with phenobarbital, using the equation PS/(1 − PS). We assessed the balance of covariates after weighting by examining the standard difference (Cohen *d*) between the groups. In a randomized clinical trial, *d* is expected to be zero for each covariate, with a standard error of $(2/n)^{1/2}$, where *n* is the size of each group.[18] We calculated *d* for each covariate. If *d* was less than 1 SE, we called the balance excellent; if *d* was between 1 and 2 SEs, good; and if *d* was more than 2 SEs, poor.

In the third analysis, we present the weighted generalized estimating equations without adjustment. This result was our final estimate.[16] In the fourth analysis, we present the weighted generalized estimating equations with adjustment by covariates.

We present odds ratios and the number needed to treat (NNT). To calculate the NNT, we assumed that children treated with phenobarbital responded at the observed, unadjusted success rate of $p1$. We used odds ratios to calculate the counterfactual probability of success had the infants been treated instead with levetiracetam ($p2$). The NNT is $1/(p2 - p1)$.

Missing Data

In the bivariate analysis, we treated "unknown" as its own category. In multivariable analysis, we used multiple imputation for missing values to avoid the bias introduced by a complete case analysis. To do so, we created and analyzed 100 data sets with imputed values and pooled the estimates. We used the fully conditional specification technique, assuming data missing at random.[19]

Sensitivity Analyses

As a check for selection bias, we repeated the analysis excluding early failures (ie, children who required a second AED within 1 week of starting the first medication). We reasoned that early failure could be a marker of difficult-to-treat epilepsy, which might be correlated with factors apparent on

presentation that were not captured in the ELES database. As a second sensitivity analysis to roughly estimate differences in efficacy, we repeated the analysis excluding infants who failed monotherapy for reasons other than for perceived efficacy (ie, adverse effects, planned wean, or unknown).

Results

During the study period, 243 children with nonsyndromic epilepsy and seizure onset between 1 month and 1 year of age were enrolled. We excluded 88 children for the following reasons: 4 received no treatment, 7 received initial polytherapy, 1 was awaiting neurosurgery for a brain tumor, 37 were treated with an AED other than levetiracetam or phenobarbital, 22 were not followed up for a minimum of 6 months after treatment initiation, 12 had insufficient information to determine freedom from seizures between 3 and 6 months, and 5 started treatment more than 1 year after the initial seizure. Of the remaining 155 children (74 boys; median age, 4.7 months [interquartile range, 3.0-7.1 months]), 117 received levetiracetam and 38 received phenobarbital. There were somewhat more children excluded among those treated with levetiracetam (34 of 151 [22.5%]) compared with those receiving phenobarbital (5 of 43 [11.6%]; $P = .18$) (**Figure 2**).

We included a median of 7 infants (range, 1-28 infants) from each of the 17 sites. Twelve sites used phenobarbital for at least 1 infant, 16 used levetiracetam for at least 1 infant, and 11 used both medications.

Target dosing information was available for 84 infants (71.8%) treated with levetiracetam and 22 infants (57.9%) treated with phenobarbital. The median target dose was 25 mg/kg/d (interquartile range, 20-33 mg/kg/d) for levetiracetam and 5 mg/kg/d (interquartile range, 4.1-5.4 mg/kg/d) for phenobarbital.

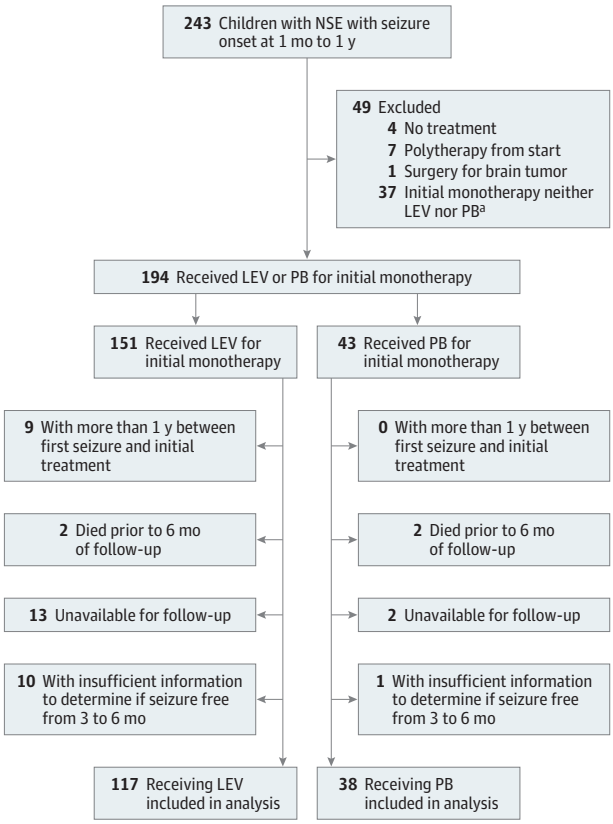
Children treated with levetiracetam were, on average, 2 months older at the time of seizure onset than children treated with phenobarbital (median, 5.2 months [interquartile range, 3.5-8.2 months] vs 3.0 months [interquartile range, 2.0-4.4 months]; $P < .001$) (**Table 1**). Children treated with levetiracetam also tended to begin treatment a longer time after the first seizure and tended to have less developmental delay at the time of epilepsy diagnosis. There were other differences that might be clinically important, although they were not statistically different. For example, the phenobarbital group had a higher proportion than the levetiracetam group with developmental structural brain abnormalities (31.6% [n = 12] vs 17.1% [n = 20]), a lower proportion with unknown possible cause (42.1% [n = 16] vs 59.8% [n = 70]), and a lower proportion with normal head circumference (68.4% [n = 26] vs 80.3% [n = 94]) (Table 1).

Weighting for observable selection bias led to excellent balance for 35 covariates, good balance for 4, and poor balance for 1 (an example in which developmental delay was unknown in the phenobarbital group for 1 child vs a weighted 0.15 children in the levetiracetam group; $d = 1.05$) (**Table 2**).

Children treated with levetiracetam were free from monotherapy failure more often than children treated with phenobarbital (47 [40.2%] vs 6 [15.8%]; $P = .01$; odds ratio, 3.6; 95% CI, 1.5-10; NNT, 4.1 [95% CI, 2.0-17]). This finding was robust to adjustment for covariates, observable selection bias, correlation of outcomes within each center, and multiple imputation for missing data (2 individuals with unknown developmental delay). Our final estimate found that levetiracetam was superior to phenobarbital (odds ratio, 4.2; 95% CI, 1.1-16; NNT, 3.5; 95% CI, 1.7-60) (**Table 3**).

In the sensitivity analyses, we found that the phenobarbital group had a higher proportion of early failures than the levetiracetam group (7 [18.4%] vs 8 [6.8%]; $P = .07$) (eFigure in the Supplement). We also found that infants failed monotherapy owing to a perceived lack of efficacy for 26 of 32 (81.3%) in the phenobarbital group and 60 of 70 (85.7%) in the levetiracetam group ($P = .80$). Both sensitivity analyses found levetiracetam superior to phenobarbital: the sensitivity analysis excluding early failures had an odds ratio of 4.8 (95% CI, 1.3-18) (eTable 1 in the Supplement), and the sensitivity analysis excluding individuals who failed monotherapy for reasons other than efficacy (ie, adverse effects, planned wean, or unknown) had an odds ratio of 3.6 (95% CI, 1.2-11) (eTable 2 in the Supplement).

Figure 2. Flow Diagram Indicating Which Participants in the Early Life Epilepsy Study Were Included in the Analyses



LEV indicates levetiracetam; NSE, nonsyndromic epilepsy; and PB, phenobarbital.

[a] A total of 37 infants were treated with oxcarbazepine (19), topiramate (8), zonisamide (5), viagabatrin (2), clobazam (1), lamotrigine (1), or phenytoin (1).

Table 1. Unweighted Bivariate Comparison of Children 1 Month to 1 Year of Age With Nonsyndromic Epilepsy Treated With Levetiracetam vs Phenobarbital

Characteristic	Children, No. (%)		*P* Value[a]
	Levetiracetam (n = 117)	Phenobarbital (n = 38)	
Demographics			
Age at onset, median (IQR), mo	5.2 (3.5-8.2)	3.0 (2.0-4.4)	<.001
Male sex	56 (47.9)	18 (47.4)	>.99
Ethnicity			
Hispanic or Latino	24 (20.5)	8 (21.1)	.94
Not Hispanic or Latino	71 (60.7)	22 (57.9)	
Unknown Hispanic or Latino	22 (18.8)	8 (21.1)	
Race			
White	76 (65.0)	25 (65.8)	.99
Black	7 (6.0)	2 (5.3)	
Other or unknown	34 (29.1)	11 (28.9)	
Premature gestational age (<37 wk)	22 (18.8)	11 (28.9)	.27
Distance from center			
Same city	24 (20.5)	7 (18.4)	.93
≤160 km	77 (65.8)	25 (65.8)	
>160 km	16 (13.7)	6 (15.8)	
Insurance			
Public	53 (45.3)	15 (39.5)	.57
Private	54 (46.2)	21 (55.3)	
Other or unknown	10 (8.5)	2 (5.3)	
Epilepsy History			
Etiology			
Developmental structural brain abnormality	20 (17.1)	12 (31.6)	.36
Neurocutaneous	4 (3.4)	1 (2.6)	
Acquired	10 (8.5)	5 (13.2)	
Genetic	8 (6.8)	3 (7.9)	
Other	5 (4.3)	1 (2.6)	
Unknown	70 (59.8)	16 (42.1)	
Time from seizure onset to first drug			
Same day	50 (42.7)	24 (63.2)	.07
≤1 wk	8 (6.8)	4 (10.5)	
1 wk to <1 mo	30 (25.6)	4 (10.5)	
1 mo to <1 y	29 (24.8)	6 (15.8)	
Seizure presentation			
Focal	66 (56.4)	23 (60.5)	.88
Generalized	29 (24.8)	8 (21.1)	
Mixed or unclear	22 (18.8)	7 (18.4)	
Neurologic History			
Head size			
Normal	94 (80.3)	26 (68.4)	.50
Microcephaly (<3rd percentile)	14 (12.0)	7 (18.4)	
Macrocephaly (>95th percentile)	7 (6.0)	4 (10.5)	
Unknown	2 (1.7)	1 (2.6)	
Developmental delay			
Definite	28 (23.9)	14 (36.8)	.06
Mild	13 (11.1)	8 (21.1)	
Normal	75 (64.1)	15 (39.5)	
Unknown	1 (0.9)	1 (2.6)	
Brain imaging findings			
Normal	47 (40.2)	12 (31.6)	.22
Equivocal	15 (12.8)	7 (18.4)	
Abnormal	38 (32.5)	17 (44.7)	
Not done	17 (14.5)	2 (5.3)	

Abbreviation: IQR, interquartile range.

[a] The χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables.

Table 2. Weighted Comparison of Children 1 Month to 1 Year of Age With Nonsyndromic Epilepsy Treated With Levetiracetam vs Phenobarbital

Characteristic	Children, No. (%)		Quality of Balance (Cohen *d*)[b]
	Phenobarbital (n = 38)	Levetiracetam (n = 37.4)[a]	
Demographic			
Age at onset, median (IQR), mo	3.0 (2.0-4.4)	2.6 (1.3-4.0)	Excellent (0.06)
Male sex	18 (47.4)	20.9 (55.9)	Excellent (0.19)
Ethnicity			
Hispanic or Latino	8 (21.1)	6.5 (17.4)	Excellent (0.13)
Not Hispanic or Latino	22 (57.9)	19.5 (52.1)	Excellent (0.13)
Unknown Hispanic or Latino	8 (21.1)	11.5 (30.7)	Good (0.28)
Race			
White	25 (65.8)	22.1 (59.1)	Excellent (0.16)
Black	2 (5.3)	1.5 (4.0)	Excellent (0.16)
Other or unknown	11 (28.9)	13.7 (36.6)	Excellent (0.19)
Premature gestational age (<37 wk)	11 (28.9)	13.3 (35.6)	Excellent (0.17)
Distance from center			
Same city	7 (18.4)	7.1 (19.0)	Excellent (0.02)
≤160 km	25 (65.8)	24 (64.2)	Excellent (0.04)
>160 km	6 (15.8)	6.4 (17.1)	Excellent (0.05)
Insurance			
Public	15 (39.5)	13.5 (36.1)	Excellent (0.08)
Private	21 (55.3)	21 (56.1)	Excellent (0.02)
Other or unknown	2 (5.3)	2.8 (7.5)	Excellent (0.21)
Epilepsy History			
Etiology			
Developmental structural brain abnormality	12 (31.6)	12.5 (33.4)	Excellent (0.05)
Neurocutaneous	1 (2.6)	1.1 (2.9)	Excellent (0.06)
Acquired	5 (13.2)	4.4 (11.8)	Excellent (0.07)
Genetic	3 (7.9)	1.5 (4.0)	Good (0.4)
Other	1 (2.6)	0.6 (1.6)	Good (0.28)
Unknown	16 (42.1)	17.4 (46.5)	Excellent (0.1)
Time from seizure onset to first drug			
Same day	24 (63.2)	23.2 (62.0)	Excellent (0.03)
≤1 wk	4 (10.5)	5.8 (15.5)	Good (0.25)
1 wk to 1 <mo	4 (10.5)	3.5 (9.4)	Excellent (0.07)
1 mo to <1 y	6 (15.8)	4.9 (13.1)	Excellent (0.12)
Seizure presentation			
Focal	23 (60.5)	21.3 (57.0)	Excellent (0.08)
Generalized	8 (21.1)	6.6 (17.6)	Excellent (0.12)
Mixed or unclear	7 (18.4)	9.5 (25.4)	Excellent (0.23)
Neurologic History			
Head size			
Normal	26 (68.4)	24.1 (64.4)	Excellent (0.1)
Microcephaly (<3rd percentile)	7 (18.4)	9.3 (24.9)	Excellent (0.21)
Macrocephaly (>95th percentile)	4 (10.5)	3.1 (8.3)	Excellent (0.15)
Unknown	1 (2.6)	0.9 (2.4)	Excellent (0.05)
Developmental delay			
Definite	14 (36.8)	15.5 (41.4)	Excellent (0.15)
Mild	8 (21.1)	6.7 (17.9)	Excellent (0.15)
Normal	15 (39.5)	15.1 (40.4)	Excellent (0.15)
Unknown	1 (2.6)	0.15 (0.4)	Poor (1.05)
Brain imaging findings			
Normal	12 (31.6)	12.9 (34.5)	Excellent (0.07)
Equivocal	7 (18.4)	5.4 (14.4)	Excellent (0.16)
Abnormal	17 (44.7)	17.3 (46.3)	Excellent (0.03)
Not done	2 (5.3)	1.7 (4.5)	Excellent (0.08)

Abbreviation: IQR, interquartile range.

[a] The effective sample size is the sum of the weights. Weighted percentages are given.

[b] One SE of *d* is $(2/n)^{1/2}$, where *n* is the size of each group. For a group size of 38, 1 SE is 0.23. If *d* is within 1 SE, the balance is excellent; if within 2, good; otherwise, poor.

Table 3. Multivariable Estimates of Freedom From Monotherapy Failure, LEV vs PB, for Children 1 Month to 1 Year of Age With Nonsyndromic Epilepsy

Statistical Model, Adjustment for Covariates[a]	OR (95% CI) of a Better Outcome for LEV vs PB	Number Needed to Treat (95% CI)
Generalized estimating equations		
No	3.6 (1.7-7.8)	4.1 (2.3-13)
Yes	3.1 (1.3-7.4)	4.8 (2.4-27)
Weighted generalized estimating equations[b]		
No	4.2 (1.1-16)	3.5 (1.7-60)
Yes	4.2 (1.3-14)	3.5 (1.7-31)

Abbreviations: LEV, levetiracetam; OR, odds ratio; PB, phenobarbital.

[a] Adjustment for age at onset, developmental delay, and time from seizure onset to first drug. Multiple imputation was used for 2 missing values of developmental delay.

[b] Weighted using propensity scores as described in the text.

Discussion

Our findings suggest that levetiracetam has superior effectiveness compared with phenobarbital as initial monotherapy for nonsyndromic epilepsy in infants. We estimate that for every 100 infants with epilepsy treated with levetiracetam instead of phenobarbital, 44 infants would be free from monotherapy failure instead of 16.

Context in the Literature

These findings provide novel evidence that may help clinicians select an initial medication for infants with nonsyndromic epilepsy. This evidence is important given that high-quality comparative effectiveness research for infantile-onset epilepsy has been limited to infantile spasms.[2,3] The findings are particularly relevant given the mismatch between current practice and regulatory approval for levetiracetam in infantile seizures. Both in our multicenter US cohort and in international practice, levetiracetam is routinely used as first-line monotherapy in infants with epilepsy,[6,7] yet the US Food and Drug Administration has not approved levetiracetam as monotherapy for any age group and has approved it only as adjunctive treatment of partial seizures in infants aged 1 month or older (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021035s089,021505s030lbl.pdf). The European Union has approved levetiracetam as monotherapy for individuals 16 years or older but has approved it only as adjunctive therapy for children as young as 1 month (http://ema.europa.eu).

There are few published data against which to compare our observations. In the only relevant randomized clinical trial that included children as young as 1 month, 43% of children with refractory focal seizures had a 50% reduction of seizures after adding levetiracetam to an existing AED regimen compared with 20% of children who received placebo.[13] That study included infants with more severe epilepsy than in our cohort in that the infants already received 1 or more other AEDs. Nevertheless, the overall 43% response rate was similar to the 40.2% success rate of levetiracetam that we found in this study. Retrospective medical record review studies have reported response rates (≥50% seizure reduction) to levetiracetam of 54%[20] and 30%[21] in populations with treatment-resistant epilepsy, rates that are also roughly similar to our findings. A recent prospective observational study found that seizures improved in 72% of infants after taking levetiracetam.[22] It is challenging, however, to interpret that study, which included patients with syndromic and nonsyndromic epilepsy, included patients treated with polytherapy, and used a subjective 7-point outcome measure.

Phenobarbital is effective for focal and generalized seizures across the age spectrum.[8] However, data supporting the use of phenobarbital for infantile-onset epilepsy are limited. A review focused on treatments for infantile seizures found only weak evidence for phenobarbital in benign infantile convulsions and no data for focal or generalized seizures.[2] The review identified only 1 comparative study, which found that carbamazepine performed better than phenobarbital in 8 patients with norovirus infection.[23]

Research Implications

A prospective clinical trial is needed. Levetiracetam and phenobarbital are both commonly used for infantile-onset epilepsy,[6,7] indicating community equipoise regarding their relative effectiveness. However, the effect size in our analysis was surprisingly large (NNT, 3.5), suggesting that a change in practice could meaningfully improve outcomes. A definitive study would need to track detailed neurodevelopmental and behavioral outcomes because uncontrolled seizures are associated with developmental decline in early-life epilepsy,[24] some data suggest a negative effect of phenobarbital on neurodevelopment,[10,25] and both medications may cause behavioral adverse effects.

International Implications

If confirmed, these findings could encourage the international community to improve access to levetiracetam in low- and middle-income countries, where more than 80% of people with epilepsy live.[26] At present, information on the international availability and pricing of levetiracetam is difficult to find because it is not included in a commonly referenced international survey of medication pricing.[27] Phenobarbital, in contrast, is on the World Health Organization list of essential medicines[28] and among the least expensive AEDs worldwide.[8,27]

Potential Mechanisms of Action

At least 3 potential mechanisms of action explain our findings. First, levetiracetam may be a more efficacious anti-seizure drug for infantile epilepsy than phenobarbital. Both γ-aminobutyric acid-A receptors[29] (the target of phenobarbital) and synaptic vesicle glycoprotein 2A[30] (the target of levetiracetam) have differential expression during development, which may cause different efficacy at different ages. Second, levetiracetam may have more antiepileptogenic properties compared with phenobarbital. Results of animal studies suggest that phenobarbital increases apoptotic neurodegeneration and alters synaptic maturation in the normally developing rat brain,[31,32] whereas levetiracetam re-

duces apoptosis in injured brain tissue and does not affect synaptic maturation.[32-34] These changes may underlie an antiepileptogenic effect for levetiracetam and/or a proepileptogenic effect for phenobarbital. Third, although the most common reason for monotherapy failure was the perception of poor efficacy, it is also possible that the findings are better explained by other factors such as tolerability, adherence, parent preferences, or titration regimens. This possibility is particularly salient given our incomplete data on medication dosing and serum drug levels.

Limitations

Several limitations merit discussion. First, PS analyses control for selection bias by observed characteristics (the factors in Table 1) but cannot account for unobserved confounders. For example, clinicians may have selected phenobarbital for children perceived as having worse epilepsy (or levetiracetam for more benign epilepsy) based on information not recorded in the ELES. Second, outcome information was missing for more infants treated with levetiracetam than those treated with phenobarbital, which may have biased our analyses. For example, children with poor seizure control may be more likely to follow up (or, alternatively, be more likely to seek care elsewhere). Third, although our analyses found strong evidence of a benefit of levetiracetam compared with phenobarbital, our estimate of the effect size remains uncertain given the wide 95% CIs in the final result. Fourth, we considered only a 6-month outcome, yet clearly longer-term outcomes are of critical interest. Fifth, nonsyndromic epilepsy is a heterogeneous group with multiple possible causes and complex genetics. Further work is needed to understand how these factors influence treatment response.

Conclusions

Levetiracetam appears to be superior to phenobarbital as initial monotherapy for infantile-onset epilepsy. Given the dearth of evidence for treating nonsyndromic early-life epilepsies and given that these are the 2 most commonly used AEDs in this population, a randomized trial comparing their effectiveness is now needed.

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