



## Research Paper

# Levetiracetam versus Phenobarbital for Neonatal Seizures: A Retrospective Cohort Study



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## ABSTRACT

**Background:** Although phenobarbital (PB) is commonly used as a first-line antiseizure medication (ASM) for neonatal seizures, in 2015 we chose to replace it with levetiracetam (LEV), a third-generation ASM. Here, we compared the safety and efficacy of LEV and PB as first-line ASM, considering the years before and after modifying our treatment protocol.

**Methods:** We conducted a retrospective cohort study of 108 neonates with electroencephalography (EEG)-confirmed seizures treated with first-line LEV or PB in 2012 to 2020.

**Results:** First-line ASM was LEV in 33 (31%) and PB in 75 (69%) neonates. The etiology included acute symptomatic seizures in 69% of cases (30% hypoxic-ischemic encephalopathy, 32% structural vascular, 6% infectious, otherwise metabolic) and neonatal epilepsy in 22% (5% structural due to brain malformation, 17% genetic). Forty-two of 108 (39%) neonates reached seizure freedom following first-line therapy. Treatment response did not vary by first-line ASM among all neonates, those with acute symptomatic seizures, or those with neonatal-onset epilepsy. Treatment response was lowest for neonates with a higher seizure frequency, particularly for those with status epilepticus versus rare seizures ( $P < 0.001$ ), irrespective of gestational age, etiology, or EEG findings. Adverse events were noted in 22 neonates treated with PB and in only one treated with LEV ( $P < 0.001$ ).

**Conclusions:** Our study suggests a potential noninferiority and a more acceptable safety profile for LEV, which may thus be a reasonable option as first-line ASM for neonatal seizures in place of PB. Treatment should be initiated as early as possible since higher seizure frequencies predispose to less favorable responses.

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## Introduction

Neonatal seizures occur in one to four of 1000 neonates,<sup>1-4</sup> with substantially higher rates reported in preterm neonates.<sup>5</sup> Neonatal seizures, particularly when recurrent or prolonged,<sup>6,7</sup> have been shown to increase the risk for neurological sequelae, including cognitive and motor impairment and postneonatal epilepsy.<sup>8-10</sup> Despite the urgent need to control neonatal seizures, there is still an open debate concerning their optimal management.<sup>11</sup> Phenobarbital (PB), the oldest and most popular first-line antiseizure medication (ASM),<sup>12</sup> displays efficacy in only half of cases<sup>13</sup> and produces the phenomenon of electroclinical uncoupling in treated

neonates.<sup>14</sup> Moreover, PB has been associated with widespread neuronal apoptosis<sup>15</sup> and impaired synaptic maturation<sup>16</sup> in the immature rat brain. The main adverse effects of PB, including hypotension, respiratory suppression, and sedation, are particularly relevant in the neonatal intensive care unit. Third-generation ASMs with a good efficacy and safety profile, particularly levetiracetam (LEV), have emerged as novel treatment options for neonatal seizures.<sup>17–22</sup>

Over the last decade, the use of PB has declined, whereas the use of LEV has increased 10-fold, as demonstrated in a US report.<sup>23</sup> One of the key arguments for LEV use in neonatal seizures is the more favorable pharmacokinetics, characterized by a linear clearance, few drug interactions, and a wide therapeutic index.<sup>24</sup> At the same time, PB is linked to autoinducible clearance with use and numerous drug interactions.<sup>25</sup> However, unequivocal evidence for the efficacy of LEV in the treatment of neonatal seizures, particularly compared with PB, is yet lacking.<sup>26,27</sup> In a recent randomized controlled study,<sup>28</sup> PB was considerably more effective than LEV for treating neonatal seizures, but higher rates of adverse effects were seen with PB treatment.<sup>28</sup> This finding of significantly poorer LEV efficacy than PB increases treatment uncertainty in neonatal seizures. Evaluating current practices is urgently needed to refine our treatment strategies and, ultimately, facilitate the best possible outcome for affected neonates.

In 2015, motivated by several studies indicating that LEV is at least as effective as PB and has lower adverse effect rates,<sup>17,21,22,29,30</sup> we modified the neonatal seizure treatment protocol in our institution and introduced LEV as first-line ASM in place of PB. In the present study, we aimed to evaluate this paradigm shift by comparing the safety and efficacy of LEV to PB as first-line ASM in electroencephalography (EEG)-confirmed neonatal seizures, considering the years before and after the modification of our treatment protocol. Our findings may shed some light on treatment options in this particularly vulnerable age group.

## Patients and Methods

### Study population

We retrospectively identified from our institutional database at the University Children's Hospital Zurich preterm and term neonates (age  $\leq 30$  days, corrected gestational age  $\leq 44$  weeks) with seizures diagnosed and treated from December 2011 to July 2020. Only neonates (1) with EEG-confirmed seizures; (2) with either LEV or PB as first-line ASM; and (3) with available informed general consent were considered for this study. We excluded neonates (1) who received first-line treatment with an ASM other than LEV or PB; and (2) whose parents had not given informed general consent. The sequence of ASM administration was determined by the currently pertinent institutional treatment protocol and the discretion of the attending physician of the neonatal intensive care unit. Abnormal neurological examination at the time of seizure manifestation was determined by abnormalities in consciousness, tone, and reflexes, as documented by the treating clinicians.

The collection of patient data and the scientific analysis were approved by and performed according to the guidelines and regulations of the local ethics committee (KEK-ZH PB-2019-01878). All parents gave informed general consent to reuse clinical data for research.

### EEG acquisition and review

Neonates underwent scalp video-EEG with 12 or 21 electrodes placed according to the international 10–20 system, depending on the infant's head circumference. Extracerebral leads were applied

for respiratory and electrocardiogram recording and surface electromyography. EEG recordings in neonates included a complete cycle of awake, quiet, and active sleep states. Whenever state changes were not distinguishable, EEGs lasted greater than or equal to one hour, according to our institutional protocol. Neonates underwent their first EEG recording within minutes to a few hours from seizure suspicion, depending on the day and time of the first event. Subsequently, neonates underwent sequential EEGs to the end of their hospitalization and continuous seizure monitoring by EEG/amplitude-integrated EEG at the discretion of the attending physician.

The EEGs were scored<sup>6,31</sup> as follows: 1, normal; 2, mildly/moderately abnormal = excess sharp activity, absence or decreased frequency of normal patterns, excessively long low-voltage periods or overall slightly decreased voltage, asymmetries in voltage or frequencies, asynchrony for age; and 3, severely abnormal = isoelectric or low-voltage invariant activity, burst-suppression pattern, permanent discontinuous activity.

### Characterization of seizures

Electrographic seizures in neonates were defined as sudden, abnormal EEG events with a repetitive and evolving pattern with a peak-to-peak voltage of  $>2$   $\mu\text{V}$  and a duration of  $>10$  seconds,<sup>32</sup> while “evolving” refers to an unequivocal evolution in frequency, voltage, morphology, or location. Seizures were classified as *electrographic only* if no clinical signs were observed by the bedside provider or on video review or as *electroclinical* if a clinical sign was associated with an ictal discharge.<sup>33</sup> Seizure etiology was classified based on the current framework for neonatal seizures and epilepsy syndromes<sup>33</sup> as hypoxic-ischemic, structural vascular (including acute ischemic stroke, hemorrhage, and other vascular induced ischemia), structural due to brain malformation, genetic, infectious, metabolic, and unknown. We further divided seizure etiology to *acute symptomatic seizures*, including hypoxic-ischemic, structural vascular, infectious, and metabolic, and *neonatal epilepsies*, including structural due to brain malformation and genetic.

Seizure frequency within the first 24 hours was determined by clinical reports, and findings of continuous monitoring by EEG/amplitude-integrated EEG if available, as (1) rare (less than five seizures); (2) occasional (five to 10 seizures); (3) frequent ( $>10$  seizures); or (4) status epilepticus, when the summed duration of seizures comprised  $\geq 50\%$  of an one-hour epoch.<sup>32</sup>

### Treatment administration and response

According to our institutional treatment protocol, neonates with seizures received infusion over 15 minutes of either LEV at 30 mg/kg or PB at 15 to 20 mg/kg, with an additional 15 minutes allowed for the ASM to take effect. If seizures persisted or recurred 30 minutes after the first infusion was complete, neonates received an extra dose of LEV at 30 mg/kg (up to a maximum dosage of 60 mg/kg) or PB at 5 mg/kg every 15 minutes (up to a maximum dosage of 40 mg/kg). If seizures persisted or recurred 30 minutes after reaching the maximum dosage of one ASM, the patient was then treated with the other ASM. First-line ASM was PB until we modified our institutional algorithm of neonatal seizure treatment in September 2015, introducing LEV as the first-line ASM. If seizures persisted after treatment with both the first-line and second-line ASMs, neonates received a third-line ASM such as midazolam, phenytoin (PHT), and lidocaine intravenously (IV), and topiramate orally. Patients given any LEV loading dose received maintenance LEV at 15 mg/kg per dose, given IV twice daily. Patients receiving PB loading doses received maintenance PB at 2.5 mg/kg per dose, given IV once daily.

Treatment response was defined as (1) complete cessation of EEG seizures following ASM administration; and (2) no administration of further ASM for seizure control. If two or more ASMs were administered before seizure cessation, the last administered ASM was defined as effective.

Adverse events were noted as the presence of hypotension; heart rate or respiratory abnormalities with need for oxygen, ventilation, or vasopressor treatment; irritability or sedation with poor feeding; and changes in laboratory parameters (complete blood cell count, electrolytes, liver enzymes, ammonia, and blood gas analysis) that were attributed to an ASM by the clinical team and documented in the medical record.

### Statistical analysis

Comparative statistics (1) for the subgroups of neonates who received LEV versus PB as first-line ASM; (2) for treatment response according to etiology; and (3) for treatment response according to dosage were performed with Fisher's exact test for categorical variables (two-sided, no correction for multiple testing) and Wilcoxon rank-sum test for continuous variables. We fitted a quasi-

Poisson generalized linear model with log link to assess the incidence risk ratio of incomplete treatment response to the first-line and second-line ASMs, respectively. We included gestational age, etiology, seizure frequency, EEG findings, and ASM as explanatory variables. We excluded nine neonates with seizures of unknown etiology from this analysis. Statistical analysis was performed with R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). We did not account for missing data in our analysis. Significance was established at  $P < 0.05$ .

## Results

### Patient characteristics

Between December 2011 and July 2020, 180 neonates were diagnosed with EEG-confirmed seizures in our institutional setting. Seventy-two (40%) neonates were excluded from our study: 34 (19%) due to first-line treatment with ASMs other than LEV or PB (mainly benzodiazepines, such as midazolam, diazepam, clonazepam) and 38 (21%) due to lack of general consent from parents (Supplementary Figure 1). The remaining 108 neonates (60 female)

**TABLE 1.**

Comparison of Clinical Features and Treatment Response in the Subgroups of Neonates Who Received LEV or PB as First-Line ASM

Clinical Features	LEV as First-Line ASM, N = 33*	PB as First-Line ASM, N = 75*	P Value <sup>†</sup>	All Neonates, N = 108*
Response			0.40	
Incomplete	18 (55%)	48 (64%)		66 (61%)
Complete	15 (45%)	27 (36%)		42 (39%)
Sex			>0.99	
Female	18 (55%)	42 (56%)		60 (56%)
Male	15 (45%)	33 (44%)		48 (44%)
Gestational age			0.42	
Preterm	4 (12%)	15 (20%)		19 (18%)
Term	29 (88%)	60 (80%)		89 (82%)
Week of gestation	39 (34–42)	38 (26–42)	0.67	39 (26–42)
Birthweight (g)	3,270 (2300–4950)	3,104 (600–4160)	0.66	3,155 (600–4950)
Cord-pH	7.21 (6.78–7.38)	7.18 (6.78–7.42)	0.44	7.19 (6.78–7.42)
Apgar score at 5 min	7 (0–10)	7 (0–10)	0.48	7 (0–10)
Etiology			0.12	
Hypoxic-ischemic	10 (30%)	22 (29%)		32 (30%)
Structural: vascular	8 (24%)	26 (35%)		34 (32%)
Structural: brain malformation	3 (9%)	2 (3%)		5 (5%)
Genetic	4 (12%)	15 (20%)		19 (17%)
Infectious	2 (6%)	4 (5%)		6 (6%)
Metabolic	0 (0%)	3 (4%)		3 (8%)
Unknown	6 (18%)	43 (4%)		9 (8%)
Seizure frequency			0.49	
Rare seizures	14 (42%)	22 (29%)		36 (33%)
Occasional seizures	6 (18%)	17 (23%)		23 (21%)
Frequent seizures	8 (24%)	17 (23%)		25 (23%)
Status epilepticus	5 (15%)	19 (25%)		24 (22%)
EEG findings			0.93	
Normal	3 (9%)	7 (9%)		10 (9%)
Mildly/moderately abnormal	3 (9%)	10 (13%)		13 (12%)
Severely abnormal	27 (82%)	58 (77%)		85 (79%)
Neurological status			0.27	
Normal	15 (45%)	24 (32%)		39 (36%)
Mildly abnormal	7 (21%)	14 (19%)		21 (19%)
Moderately/severely abnormal	11 (33%)	37 (49%)		48 (44%)

#### Abbreviations:

ASM = Antiseizure medication

CI = Confidence interval

EEG = Electroencephalography

IRR = Incidence rate ratio

LEV = Levetiracetam

N = Number of patients

PB = Phenobarbital

The two subgroups did not differ significantly as to any of their clinical features or as to treatment response. Summary statistics of our cohort, including counts and percentages for categorical variables, mean and range for continuous variables. Percentages are given column-wise.

\* n (%); Mean (Range).

† Wilcoxon rank sum test; Fisher's exact test.

who received as first-line ASM LEV in 33 (31%) or PB in 75 (69%) cases were enrolled in our study (Table 1).

Eighty-nine (82%) of the neonates were term and 19 (18%) were preterm (<37 weeks of gestational age); 69% of neonates had acute symptomatic seizures, including 30% hypoxic-ischemic (treated with therapeutic hypothermia in 18 of 32 cases), 32% structural vascular (12% acute ischemic stroke, 15% hemorrhage, 3% vascular-induced ischemia related to cardiac surgery and 2% to head trauma), 6% infectious, and 3% metabolic. About 22% of neonates had neonatal-onset epilepsy, including 17% genetic and 5% structural due to brain malformation. In 9% of cases, seizure etiology remained unknown. The two subgroups that received as first-line ASM LEV or PB did not differ significantly as to any of their clinical features (Table 1).

Treatment response according to etiology

Among all neonates with seizures (n = 108), only 39% reached seizure freedom following first-line therapy: treatment response did not vary by ASM (P = 0.40, Fig. 1).

Among neonates with acute symptomatic seizures (n = 75), only 39% reached seizure freedom following first-line therapy: treatment response did not vary by ASM (P = 0.59, Fig. 2A). Specifically, in hypoxic-ischemic encephalopathy (N = 32), 44% neonates reached seizure freedom after the first-line ASM: treatment response did not vary by ASM (P = 0.71, Fig. 2B). Treatment response in hypoxic-ischemic encephalopathy did not vary depending on the use of therapeutic hypothermia in the overall group (P = 0.73) or in the subgroups of neonates who received LEV or PB as first-line ASM (P > 0.99 and P = 0.67, respectively).

Treatment response according to dosage

The highest administered dosage of both LEV and PB as first-line ASM did not differ significantly between neonates with an incomplete and complete response (Wilcoxon rank-sum test, LEV: P = 0.29, PB: P = 0.06, Fig. 3).

Treatment response according to seizure frequency

The risk for incomplete response to the first-line ASM was 2.22, 3.26, and 3.53 times higher for occasional seizures (P = 0.01), frequent seizures (P < 0.001), and status epilepticus (P < 0.001) compared with rare seizures, based on the generalized linear model (Fig. 4, Table 2). Treatment outcome risks did not differ significantly by gestational age, etiology, EEG findings, or ASM.

Adverse events

Adverse events were noted in 22 (24%) of the neonates treated with PB and in only one (1%) of those treated with LEV (P < 0.001).

Discussion

Treatment response to the first-line ASM in neonates with EEG-confirmed seizures was overall low in our study and did not differ between LEV and PB among all neonates, or among those with acute symptomatic seizures and neonatal-onset epilepsy. Treatment response was lowest for neonates with a higher seizure frequency but did not differ by gestational age, etiology, or EEG findings. The adverse effect profile of LEV was more favorable compared with that of PB. Our study thus suggests that LEV may be a safe and effective alternative to PB as a first-line ASM in treating neonatal seizures.

ASM efficacy

Seizures ceased after administration of LEV or PB as first-line ASM in less than one-half of neonates and as first- and second-line ASM combined in just over one-half of neonates, reflecting the results of the clinical trial of PB versus PHT<sup>13</sup> performed over 20 years ago. These findings underline the still unmet need for effective therapies in neonatal seizures, despite the introduction of newer ASM in the last two decades.<sup>18,34,35</sup> The low first-line ASM efficacy of both LEV (45%) and PB (36%) in our study is in line with contemporary real-world data<sup>36</sup> but stands in contrast with the

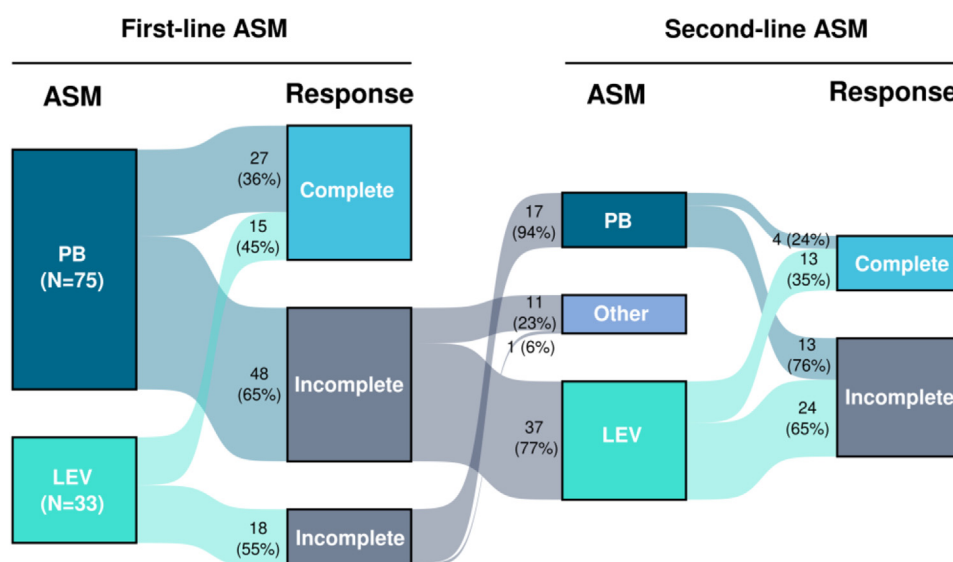
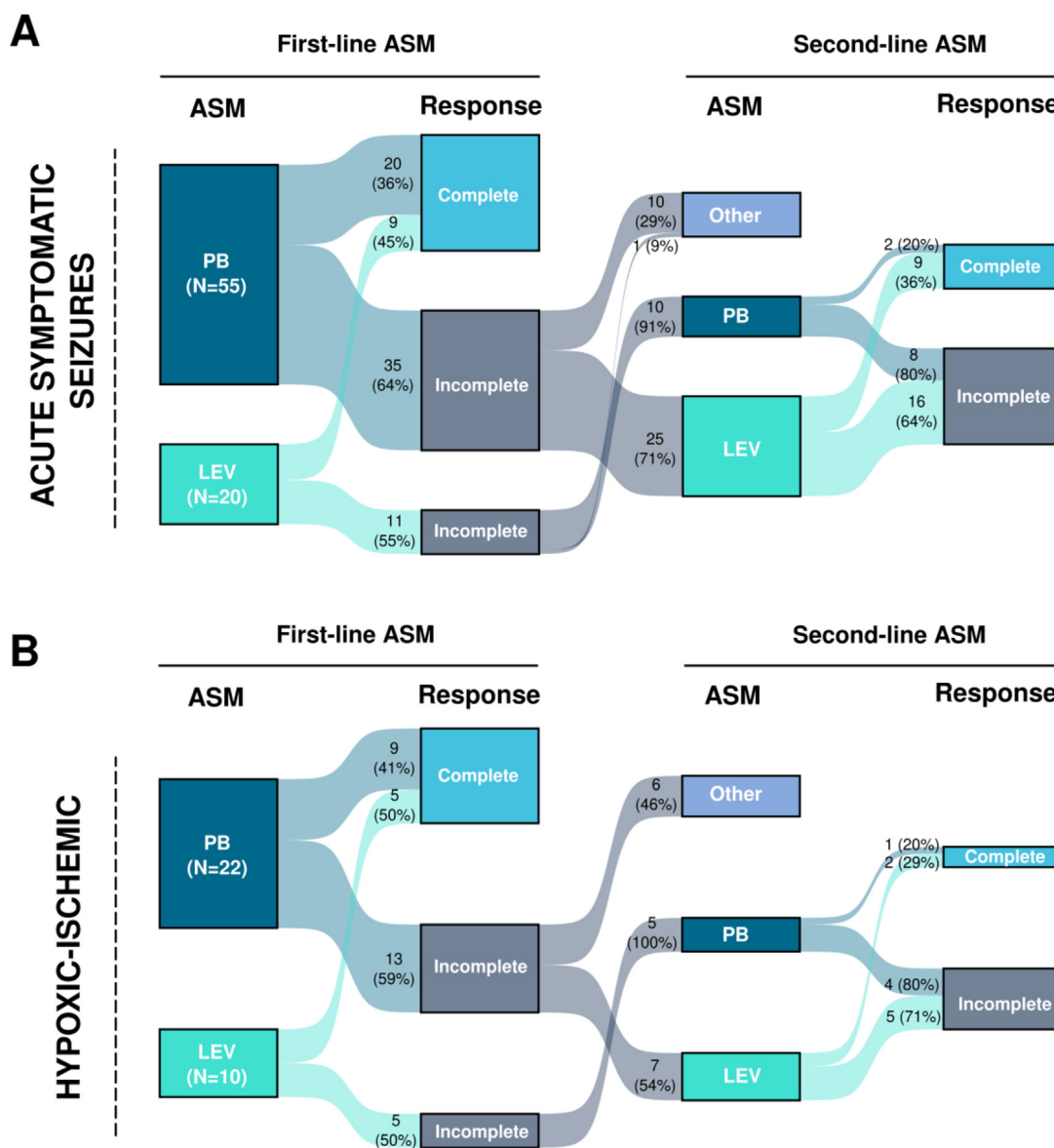


FIGURE 1. Overall treatment response. Among all neonates with seizures, only 42 of 108 (39%) reached seizure freedom following first-line therapy: treatment response did not vary by ASM (LEV, 15 of 33 = 45%; PB, 27 of 75 = 36%; P = 0.40). Of the 18 neonates who did not respond to LEV as first-line therapy, 17 received PB as second-line ASM with seizure cessation in four (24%), with a total response to both ASM in 19 of 33 (58%). Of the 48 neonates who did not respond to PB as first-line therapy, 37 received LEV as second-line ASM with seizure cessation in 13 (35%), with a total response to both ASMs in 40 of 75 (53%). Overall, seizure control had been obtained in 59 (55%) of neonates following first- and second-line therapy with LEV and PB. ASM, antiseizure medication; LEV, levetiracetam; PB, phenobarbital. The color version of this figure is available in the online edition.



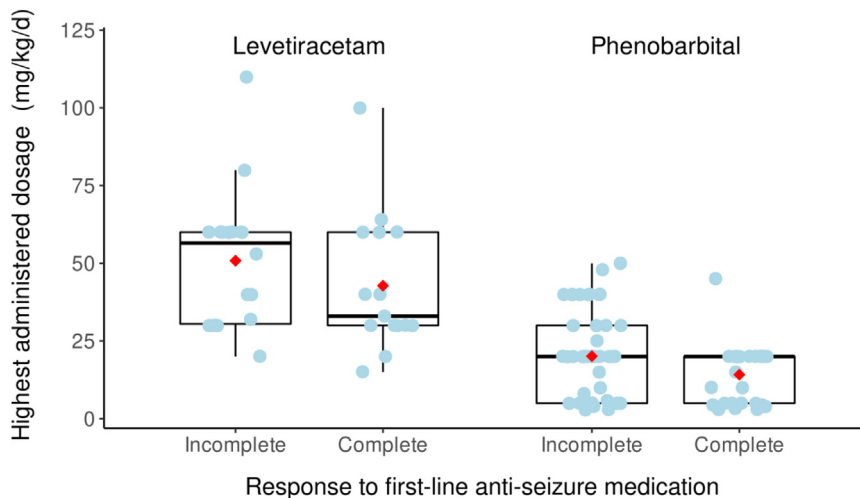
**FIGURE 2.** Treatment response according to etiology. (A) Among neonates with acute symptomatic seizures (n = 75), only 29 of 75 = 39% reached seizure freedom following first-line therapy: treatment response did not vary by ASM (LEV, nine of 20 = 45%; PB, 20 of 55 = 37%; P = 0.59). (B) Among neonates with seizures due to hypoxic-ischemic encephalopathy (N = 32), only 44% neonates reached seizure freedom after the first-line ASM: treatment response did not vary by ASM (LEV, five of 10 = 50%; PB, nine of 22 = 41%; P = 0.71). ASM, antiseizure medication; LEV, levetiracetam; PB, phenobarbital. The color version of this figure is available in the online edition.

much higher efficacy of PB (80%) in a recent multicenter randomized trial.<sup>28</sup> Higher seizure control rates in that clinical trial<sup>28</sup> may be attributed to the implementation of continuous video-EEG for early seizure identification in neonates at risk, thus enabling timely treatment initiation that can considerably improve ASM efficacy.<sup>37,38</sup> However, continuous video-EEG monitoring is unattainable in the daily clinical practice, despite the recent technological advances, including the remote review of video-EEG and the development of automated neonatal seizure detection algorithms.<sup>28,39</sup> Chief obstacles remain EEG electrode placement to start monitoring and the availability of real-time expert review of suspect events captured by video-EEG.<sup>39</sup>

Treatment response to the first-line ASM in neonates with seizures of various etiologies and, specifically, with acute symptomatic seizures did not differ between LEV and PB in our study, in line with previous observations.<sup>34,40</sup> It should be noted that seizures were acute symptomatic in over two-thirds of our cohort, consistent

with large population studies,<sup>41</sup> and that the findings in neonates with hypoxic-ischemic encephalopathy support the generalizability of our results to that crucial patient group. Our findings of equal though incomplete efficacy of LEV and PB are in line with a recent systematic review<sup>27</sup> and a later meta-analysis<sup>42</sup> that showed no difference in efficacy between LEV and PB in treating neonatal seizures. However, it should be noted that these analyses considered studies that differed as to the criteria for neonatal seizure diagnosis and treatment response,<sup>27,42</sup> whereas only few studies have employed continuous video-EEG for treatment initiation and monitoring or followed the requirements of a randomized controlled trial. The disparity in study design may at least partly account for the divergent results between our study (and other past studies) and the recent trial that reported a considerably higher efficacy for PB than for LEV.<sup>28</sup>

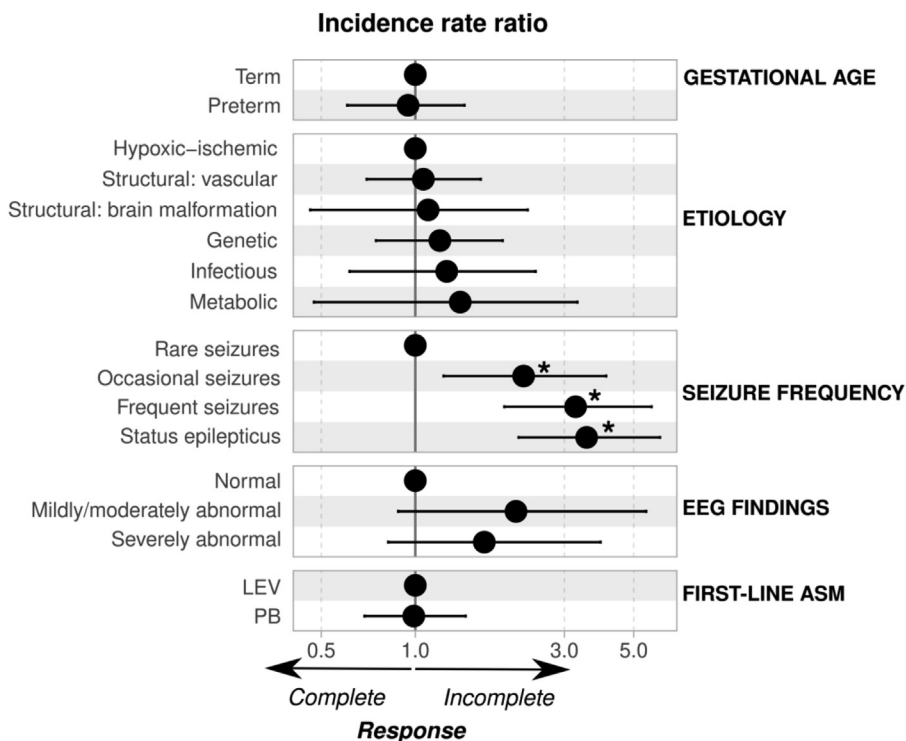
Neonates with a higher seizure frequency in our study were less likely to respond to the first-line ASM. In contrast, treatment



**FIGURE 3.** Highest administered dosage of the first-line antiseizure medication (ASM) to the 108 neonates with seizures treated with levetiracetam (LEV) or phenobarbital (PB), stratified by first-line ASM response. The red rhombus depicts the mean, and the bold black lines depict the median in each boxplot. The highest administered dose of LEV did not differ significantly between neonates with complete response (mean  $\pm$  S.D.:  $42.8 \pm 22.1$  mg/kg, Wilcoxon rank-sum test,  $P = 0.29$ ) and incomplete response ( $50.8 \pm 22.0$  mg/kg). Similarly, the highest administered dose of PB did not differ significantly between neonates with complete response ( $14.2 \pm 9.7$  mg/kg, Wilcoxon rank-sum test,  $P = 0.06$ ) and incomplete response ( $20.1 \pm 14.0$  mg/kg). The color version of this figure is available in the online edition.

response did not differ by gestational age, etiology, or EEG findings, in line with previous reports.<sup>13,18,34</sup> Ever since the clinical trial of PB versus PHT,<sup>13</sup> it has been noted that the likelihood of treatment success in neonatal seizures decreases with increasing seizure frequency. This observation should be considered when comparing ASM efficacy in our study with the recent trial that identified seizures by continuous video-EEG,<sup>28</sup> thus including patients at seizure onset, and with a yet low seizure frequency. High seizure frequency,

with status epilepticus and frequent seizures in one-fourth each of our cohort, may at least partly account for the relatively low rates of seizure cessation after first-line ASM administration in our study, compared with previous work.<sup>18,28</sup> Interestingly, higher ASM doses were not linked to improved efficacy in our cohort, although some neonates received LEV dosages higher than the licensed 60 mg/kg/day that have recently been shown to improve seizure control.<sup>43</sup> Although it is tempting to try higher doses, particularly of LEV,



**FIGURE 4.** Incidence rate ratios of the variables that determined the response to the first-line ASM based on the generalized linear model. In a fitted regression model including gestational age, etiology, seizure frequency, EEG findings, and first-line ASM, only higher seizure frequency (occasional seizures, frequent seizures, status epilepticus) was associated with a less favorable response to the first-line ASM ( $P < 0.05$ ). ASM, antiseizure medication; EEG, electroencephalography; LEV, levetiracetam; PB, phenobarbital. \*Statistical significance,  $P < 0.05$ . The color version of this figure is available in the online edition.

**TABLE 2.**  
Response to the First-Line and Second-Line ASMs According to the Clinical Features of the Patients and to the Respective ASM: Multivariate Analysis

Clinical Features	First-Line ASM				Second-Line ASM			
	N	IRR	95% CI	P Value	N	IRR	95% CI	P Value
Gestational age								
Term	81	—	—		41	—	—	
Preterm	18	0.95	0.61, 1.44	0.81	10	0.96	0.48, 1.83	0.91
Etiology								
Hypoxic-ischemic	32	—	—		12	—	—	
Structural: vascular	34	1.06	0.70, 1.62	0.78	17	0.80	0.44, 1.48	0.48
Structural: brain malformation	5	1.10	0.46, 2.29	0.82	2	0.54	0.10, 1.87	0.40
Genetic	19	1.20	0.75, 1.90	0.45	14	1.03	0.55, 1.95	0.92
Infectious	6	1.26	0.62, 2.43	0.51	4	0.57	0.17, 1.56	0.31
Metabolic	3	1.39	0.47, 3.30	0.50	2	0.86	0.16, 2.92	0.84
Seizure frequency								
Rare seizures	30	—	—		6	—	—	
Occasional seizures	22	2.22	1.23, 4.08	0.010	8	3.25	0.80, 19.3	0.14
Frequent seizures	23	3.26	1.93, 5.71	<0.001	18	4.95	1.44, 27.1	0.032*
Status epilepticus	24	3.53	2.14, 6.07	<0.001	19	6.22	1.89, 33.5	0.013*
EEG findings								
Normal	8	—	—		2	—	—	
Mildly/moderately abnormal								
Severely abnormal								
First-line ASM								
LEV	27	—	—					
PB	72	0.99	0.69, 1.45	0.95				
Second-line ASM								
LEV					36	—	—	
PB					15	1.23	0.73, 2.05	0.43

**Abbreviations:**

ASM = Antiseizure medication

EEG = Electroencephalography

LEV = Levetiracetam

N = Number of patients

PB = Phenobarbital

In a fitted regression model including gestational age, etiology, seizure frequency, EEG findings, and ASM, only seizure frequency remained significantly associated with the response to first-line and second-line ASMs ( $P < 0.05$ ). To be noted: in the first-line ASM column, nine patients with unknown seizure etiology were excluded, and in the second-line ASM column, only patients receiving PB or LEV as second-line ASM were included.

\* Statistical significance,  $P < 0.05$ .

due to its favorable safety profile, to overcome incomplete seizure response, this should not lead to unnecessary delays in treatment with other, potentially effective ASM.

**ASM adverse events**

Adverse events, including hypotension, respiratory suppression, and sedation, were noted in one-fourth of neonates treated with PB and only in a single case of those treated with LEV. Our study thus supports a more favorable adverse effect profile of LEV than PB, in line with previous work.<sup>18,28</sup> In particular, hypotension attributed to PB administration has been reported in one-half of treated neonates with hypoxic-ischemic encephalopathy<sup>44</sup> and one-sixth of treated neonates with seizures related to cardiac surgery.<sup>18</sup> Hypotension and respiratory depression following PB administration are alarming side effects in neonates with hemodynamic instability, requiring necessary adaptations of treatment management. In contrast, LEV has an excellent safety profile. It has not been associated with any serious adverse effects in numerous clinical studies, including those employing high doses for neonatal seizure control.<sup>17,20,21,43,45,46</sup> Our study thus verifies a crucial difference in the safety profile of LEV compared with PB that has been previously noted in the recent randomized controlled trial of neonatal seizure treatment<sup>28</sup> but failed to reach statistical significance in that cohort. It should be noted that the administration of PB had not been associated with any changes in heart rate, heart rhythm, mean arterial pressure, or respiratory status in the clinical trial of PB versus PHT.<sup>13</sup> This observation leads to think that therapeutic hypothermia and concurrent morphine treatment as the current

standard of care may at least partly exacerbate the side effects of PB.<sup>28</sup>

**Limitations**

Although our findings derive from a large, well-studied cohort, with EEG confirmation of neonatal seizures, first-line treatment with either LEV or PB, and inclusion of many important clinical characteristics for analysis, our study still has several limitations. First, the size of our cohort and the retrospective design of our study may have prevented the identification of specific subgroups that may have shown an optimal response to a particular ASM. However, our results are overall consistent with other contemporary multicentric studies and with recent meta-analyses, supporting the generalizability of our findings. Second, by considering only neonates with EEG-confirmed seizures we may have introduced a bias toward a higher seizure frequency, considering the sampling limitations of routine EEG recordings. Studies deriving from continuous video-EEG monitoring are bound to include neonates with less abundant seizure activity that may show a more favorable response to ASM.<sup>28</sup> Third, the precise latency from seizure manifestation to treatment initiation and treatment response in our study remained unknown due to the lack of continuous video-EEG monitoring. However, this latency may prove crucial for ASM efficacy in neonatal seizures.<sup>28</sup> Fourth, ASM use was not randomized in our study that originated from a change in our institutional protocol. Since the choice of first-line ASM depended on the treating physician's decision, it cannot be ruled out that a higher proportion of more severely affected neonates received PB as first-line ASM for

presumably difficult-to-treat seizures and that this bias may have negatively impacted PB efficacy in our study. Finally, more than one-third of neonates with EEG-confirmed seizures who received ASM treatment in our institution could not be included in our study due to first-line treatment with ASM other than LEV or PB or due to lack of general consent from parents. It cannot be ruled out that the personal preference of physicians for benzodiazepines and the personal decision of parents to refuse informed general consent may account for a selection bias in our study.

Despite these limitations, the findings of our retrospective cohort study have significant implications for neonatal seizure management since they offer crucial and complementary knowledge deriving from a real-world clinical setting. In contrast to previous studies, our findings stem from a neonatal cohort with EEG-confirmed seizures,<sup>47,48</sup> treated with first-line LEV or PB in a standardized dosage,<sup>21,22,29,30</sup> and enable the comparison of LEV versus PB in sizeable subgroups that do not differ significantly as to their key clinical features. Furthermore, our study addresses the impact of these clinical features such as gestational age, seizure etiology, EEG findings, and seizure frequency, on treatment response, in addition to the first-line ASM.

## Conclusion

PB was associated with more adverse events than LEV, and the two ASMs were equally but incompletely effective in treating neonatal seizures. Our findings suggest that LEV may be a safe and effective alternative to PB as a first-line therapy in these neonates. Treatment of EEG-confirmed neonatal seizures should be initiated as early as possible considering that a higher seizure frequency predisposes to a less favorable response. In future studies, further subgroup analyses of treatment response may shed some light on the efficacy of LEV versus PB in specific settings. Long-term follow-up analyses in infants previously treated with LEV versus PB for neonatal seizures are crucial to address the impact of these ASMs on long-term seizure and cognitive outcomes.

## Data Sharing

Source code and data necessary for the replication of our results and figures will be available at publication.

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## Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.pediatrneurol.2022.10.004>.

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