



Pick Your Poison but Pick It Wisely: Choosing a Second-Line Medication for the Management of Status Epilepticus

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Efficacy of Levetiracetam, Fosphenytoin, and Valproate for Established Status Epilepticus by Age Group (ESETT): A Double-Blind, Responsive-Adaptive, Randomised Controlled Trial

Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, Rogers A, Barsan W, Cloyd J, Lowenstein D, Bleck TP, Conwit R, Meinzer C, Cock H, Fountain NB, Underwood E, Connor JT, and Silbergleit R, Neurological Emergencies Treatment Trials; Pediatric Emergency Care Applied Research Network investigators. *Lancet*. 2020;395(10231):1217-1224. doi:<https://eur01.safelinks.com/med/32203691>

Background: Benzodiazepine-refractory, or established, status epilepticus is thought to be of similar pathophysiology in children and adults, but differences in underlying etiology and pharmacodynamics might differentially affect response to therapy. In the Established Status Epilepticus Treatment Trial (ESETT), we compared the efficacy and safety of levetiracetam, fosphenytoin, and valproate in established status epilepticus, and here, we describe our results after extending enrolment in children to compare outcomes in 3 age groups. **Methods:** In this multicenter, double-blind, response-adaptive, randomized controlled trial, we recruited patients from 58 hospital emergency departments across the United States. Patients were eligible for inclusion if they were aged 2 years or older, had been treated for a generalized convulsive seizure of longer than 5 min duration with adequate doses of benzodiazepines, and continued to have persistent or recurrent convulsions in the emergency department for at least 5 min and no more than 30 minutes after the last dose of benzodiazepine. Patients were randomly assigned in a response-adaptive manner, using Bayesian methods, and stratified by age-group (<18 years, 18-65 years, and >65 years), to levetiracetam, fosphenytoin, or valproate. All patients, investigators, study staff, and pharmacists were masked to treatment allocation. The primary outcome was absence of clinically apparent seizures with improved consciousness and without additional anti-seizure medication at 1 hour from start of drug infusion. The primary safety outcome was life-threatening hypotension or cardiac arrhythmia. The efficacy and safety outcomes were analyzed by intention to treat. This study is registered in ClinicalTrials.gov, NCT01960075. **Findings:** Between November 3, 2015, and December 29, 2018, we enrolled 478 patients and 462 unique patients were included: 225 children (aged <18 years), 186 adults (18-65 years), and 51 older adults (>65 years). One hundred seventy-five (38%) patients were randomly assigned to levetiracetam, 142 (31%) to fosphenytoin, and 145 (31%) were to valproate. Baseline characteristics were balanced across treatments within age groups. The primary efficacy outcome was met in those treated with levetiracetam for 52% (95% credible interval 41-62) of children, 44% (33-55) of adults, and 37% (19-59) of older adults; with fosphenytoin in 49% (38-61) of children, 46% (34-59) of adults, and 35% (17-59) of older adults; and with valproate in 52% (41-63) of children, 46% (34-58) of adults, and 47% (25-70) of older adults. No differences were detected in efficacy or primary safety outcome by drug within each age-group. With the exception of endotracheal intubation in children, secondary safety outcomes did not significantly differ by drug within each age-group. **Interpretation:** Children, adults, and older adults with established status epilepticus respond similarly to levetiracetam, fosphenytoin, and valproate, with treatment success in approximately half of patients. Any of the 3 drugs can be considered as a potential first-choice, second-line drug for benzodiazepine-refractory status epilepticus.


Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus

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Background: The choice of drugs for patients with status epilepticus that is refractory to treatment with benzodiazepines has not been thoroughly studied. **Methods:** In a randomized, blinded, adaptive trial, we compared the efficacy and safety of 3 intravenous anticonvulsive agents—levetiracetam, fosphenytoin, and valproate—in children and adults with convulsive status



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epilepticus that was unresponsive to treatment with benzodiazepines. The primary outcome was absence of clinically evident seizures and improvement in the level of consciousness by 60 minutes after the start of drug infusion, without additional anticonvulsant medication. The posterior probabilities that each drug was the most or least effective were calculated. Safety outcomes included life-threatening hypotension or cardiac arrhythmia, endotracheal intubation, seizure recurrence, and death. Results: A total of 384 patients were enrolled and randomly assigned to receive levetiracetam (145 patients), fosphenytoin (118), or valproate (121). Reenrollment of patients with a second episode of status epilepticus accounted for 16 additional instances of randomization. In accordance with a prespecified stopping rule for futility of finding one drug to be superior or inferior, a planned interim analysis led to the trial being stopped. Of the enrolled patients, 10% were determined to have had psychogenic seizures. The primary outcome of cessation of status epilepticus and improvement in the level of consciousness at 60 minutes occurred in 68 patients assigned to levetiracetam (47%; 95% credible interval, 39-55), 53 patients assigned to fosphenytoin (45%; 95% credible interval, 36-54), and 56 patients assigned to valproate (46%; 95% credible interval, 38-55). The posterior probability that each drug was the most effective was 0.41, 0.24, and 0.35, respectively. Numerically, more episodes of hypotension and intubation occurred in the fosphenytoin group and more deaths occurred in the levetiracetam group than in the other groups, but these differences were not significant. Conclusions: In the context of benzodiazepine-refractory convulsive status epilepticus, the anticonvulsant drugs levetiracetam, fosphenytoin, and valproate each led to seizure cessation and improved alertness by 60 minutes in approximately half the patients, and the 3 drugs were associated with similar incidences of adverse events (Funded by the National Institute of Neurological Disorders and Stroke; ESETT ClinicalTrials.gov number, NCT01960075).

Commentary

Status epilepticus (SE) is a neurologic emergency with elevated mortality rates of over 20% in adults and 3% to 6% in children.^{1,2} The International League Against Epilepsy introduced a new definition and classification of SE in 2015,³ which highlights the severity of this condition, its long-term consequences in terms of neuronal death, and irreversible brain damage as well as the urgency to treat it. The operational dimensions of this classification considers generalized motor SE as more acutely threatening for long-term damage than focal or absence SE. Higher mortality rates are seen in prolonged and progressively refractory SE. Controlling ongoing clinical seizures as well as nonconvulsive SE (NCSE) in the shortest amount of time is an urgent priority.

The first-line treatment of SE is a benzodiazepine. Lorazepam has shown efficacy and ease of use superior to other anti-seizure medications (ASM).⁴ More recently, the use of intramuscular midazolam was shown to be as effective as intravenous lorazepam, to have similar rate of complications including need for intubation, and to be easier to use in the prehospital management of SE.⁵ Benzodiazepines are effective in 60% to 70% of cases when adequate doses are used; unfortunately, they are often underdosed in the emergency department setting.⁶

Evidence for the choice of second-line ASM in SE was not clear before the publication of the trials highlighted. A meta-analysis comparing 5 ASM showed comparable efficacy in achieving seizure cessation for levetiracetam and phenobarbital, a more robust response for valproic acid, and slightly lower efficacy for phenytoin.⁷ Lacosamide was also included, but ultimately not analyzed as there were insufficient data available. Two open-label trials had recently compared the efficacy of phenytoin and levetiracetam as

second-line treatment of SE in children. The ConSEPT⁸ trial showed a slightly better performance of phenytoin (60% vs 50%), and EcLiPSE⁹ showed no significant difference in effectiveness.

Established Status Epilepticus Treatment Trial (ESETT)¹⁰ was a prospective, multicenter randomized, double-blind, adaptive trial that evaluated the efficacy and safety of 3 frequently used ASM, at adequate doses, in the management of SE refractory to benzodiazepines. This landmark study compared the use of fosphenytoin dosed at 20-mg PE/kg (maximum 1500 PE), levetiracetam dosed at 60 mg/kg (maximum 4500 mg), and valproic acid dosed at 40 mg/kg (maximum 3000 mg) in IV infusion. The main outcome was the cessation of clinical seizures (including subtle or focal seizures) 1 hour after the trial medication was administered in addition to observed improvement in alertness and responsiveness. Safety outcomes included life-threatening hypotension and cardiac arrhythmia during the hour following infusion as well as other serious adverse events within the time of hospitalization or 30 days after enrollment.

ESETT found no significant differences in efficacy or safety between the use of fosphenytoin (45% effective), levetiracetam (47% effective), and valproic acid (46% effective). A scheduled interim analysis of the data showed a less than 1% chance of finding a difference between the treatment groups which prompted the study to stop recruitment earlier than originally planned. This initial analysis of the data did not demonstrate futility within the pediatric population so the collection was expanded to enrich the pediatric group and compare the performance of these ASM by age group.¹¹ This following publication also showed no difference in efficacy or safety for all 3 age groups studied (children <18 years/old, younger adults 18-65 years, and older adults >65 years old).



Respiratory depression and need for endotracheal intubation were slightly more frequent in children who received fosphenytoin with no significant differences observed in overall safety outcomes.

Of the approximately 50% of patients who did not show improvement with the initial medication trial, 70% received additional ASM and 25% showed clinical seizure cessation but not improvement in responsiveness raising the possibility of NCSE. In the absence of electroencephalography (EEG) to rule out NCSE, the authors were wise to include improved awareness and responsiveness to the efficacy outcome target. However, descriptions of improvement in mental status were broad and subjective. The standard of care for the diagnosis and monitoring of treatment of NCSE is long-term EEG, but having immediate access to EEG is difficult in the ER environment. Emerging technologies are looking to bridge this gap and allow immediate access to EEG in settings where it was not previously available.¹² Electroencephalography also helps in the diagnosis of psychogenic non-epileptic seizures and SE which is a frequent cause of poor response to first- and second-line therapy. Making the diagnosis of PNES in the acute setting prevents unnecessary interventions and iatrogenic complications.

While ESETT provides high-level evidence regarding the choice of ASM in the management of SE in all age groups, other considerations may come into place when making this decision. If all 3 alternatives are equally safe and effective, we need to rather think about the long-term effects of committing a patient to these therapies. Keeping in mind that ASM are often easy to start and difficult to discontinue, considerations such as sex, medical comorbidities, pharmacologic interactions with other chronic therapies, and neuropsychiatric profile may sway the decision one way or another. Practical examples include avoiding valproic acid when treating a woman of childbearing age or fosphenytoin in patients with cardiovascular disease on chronic anticoagulation, among others.

The cause of SE may be another variable to consider. In patients with chronic epilepsy who present with medication noncompliance as the precipitating factor for SE, using the same medication the patient missed at a loading dose may result in a more sustainable therapy than adding a new medication to a patient who already had compliance issues. Checking ASM levels is useful to understand the cause of SE, even if these results will not be readily available for the acute treating team. Although SE is an emergency and clinical decisions are made within a narrow window of time, the decisions we make may become difficult to undo in the longer term. The good news is: all 3 of these medications seem to be equally effective. We have then the responsibility of choosing wisely for each patient. The information needed, such as demographics, prior history of epilepsy, home ASM doses, and potential noncompliance as well as medical and psychiatric comorbidities, is often readily available.

Since ESETT enrollment and publication, other medications have become available that are suitable for ER use in this

critical situation, including lacosamide and brivaracetam as well as others coming into the market. Having a strong level of evidence of efficacy and safety for the therapies that we use is an advantage. Other medications will have to measure themselves to this standard.

One last thought is for the 40% or so of patients with established convulsive SE who do not respond to the second-line ASM. One option is to add a different second-line (now third) agent. Alternatively, considering the potential long-term damage and high mortality associated with refractory SE, moving faster to general anesthesia¹³ under continuous EEG monitoring may be the clear next step. Further studies are needed to evaluate this intervention.


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