Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department with Seizures

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From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Seizures:

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ABSTRACT

This clinical policy from the American College of Emergency Physicians addresses key issues in the evaluation and management of adult emergency department patients presenting with seizure. A writing committee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical-question: In emergency department patients with generalized convulsive status epilepticus who continue to have seizures despite receiving optimal dosing of benzodiazepine, which agent or agents should be administered next to terminate seizures? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Seizure is a presentation that emergency physicians will manage, accounting for about 1% of all emergency department (ED) visits.[1,2] First-line treatment for recurrent seizures is the appropriate dosing of benzodiazepines with second-line treatment including agents such as phenytoin, levetiracetam, and valproic acid. Status epilepticus is defined as a seizure lasting longer than 5 minutes or multiple seizures without a return to neurologic baseline. Management can be clinically challenging in discerning postictal patients from those suffering from sub-clinical nonconvulsive status epilepticus and potentially lacking real time electroencephalogram monitoring in the ED. Furthermore, noncompliance with antiepileptic drug therapy may make the patient more likely to present to the ED with seizure. An additional complication is that prescribed (example: tramadol) and illicit substance use (example: cocaine) can lower the seizure threshold. Compounding this may be the time needed to obtain quantitative levels of antiepileptic medications in real time.

The 2014 ACEP clinical policy "Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Seizures," addressed several critical questions in emergency seizure evaluation and management.[3] Included in these questions, was the question "In ED patients with generalized convulsive status epileptics who continue to have seizures despite receiving optimal dosing of a benzodiazepine, which agent or agents should be administered next to terminate seizures?". After careful consideration, the Clinical Policies Committee agreed that an update to this question was appropriate. The committee also agreed that the other questions on treatment of a first seizure, the need for admission for a first

seizure where the patient has returned to baseline, and the route of administration for resuming a patient's medications were adequately addressed by the prior clinical policy.

This current policy readdresses the appropriate second-line agents in patients with refractory seizures in the emergency department that have been appropriately dosed with benzodiazepines.

METHODOLOGY

This ACEP clinical policy was developed by emergency physicians with input from medical librarians and a patient safety advocate and is based on a systematic review and critical, descriptive analysis of the medical literature and is reported in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[4]

Search and Study Selection

This clinical policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of PubMed, SCOPUS, Embase, Web of Science, and the Cochrane Database of Systematic Reviews were performed by a librarian. Search terms and strategies were peer reviewed by a second librarian. All searches were limited to human studies published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under the critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

Using Covidence (Covidence, Melbourne, Australia), two subcommittee members independently reviewed the identified abstracts to assess for possible inclusion. Of those identified for potential inclusion, each full-length text was reviewed for eligibility. Those identified as eligible were subsequently abstracted and forwarded to the committee's methodology group (emergency physicians with specific research methodological expertise) for methodological grading using a Class of Evidence framework (Appendix E1).

Assessment of Risk of Bias and Determination of Classes of Evidence

Each study identified as eligible by the subcommittee was independently graded by two methodologists..

Design 1 represents the strongest possible study design to answer the critical question, which relates to whether the focus was therapeutic, diagnostic, or prognostic, or a meta-analysis. Subsequent design types (ie, Design 2 and Design 3) represent respectively weaker study designs. Articles are then graded on dimensions related to the study's methodological features and execution, including but not limited to randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and potential for conflicts of interest.

Using a predetermined process that combines the study's design, methodological quality, and applicability to the critical question, two methodologists independently assigned a preliminary Class of Evidence grade for each article. Articles with concordant grades from both methodologists received that grade as their final grade. Any discordance in the preliminary grades was adjudicated through discussion which involved at least one additional methodologist, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix E2). Studies identified with significant methodologic limitations and/or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of evidence. Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence for the critical question, the subcommittee drafted the recommendations and supporting text synthesizing the evidence using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of scientific certainty (eg, based on evidence from one or more Class of Evidence I, or multiple Class of Evidence II studies that demonstrate consistent effects or estimates).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate scientific certainty (eg, based on evidence from one or more Class of Evidence II studies, or multiple Class of Evidence III studies that demonstrate consistent effects or estimates).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as consistency of results, uncertainty of effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations. When possible, clinically-oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient. This can assist the clinician in applying the recommendations to most patients but allow adjustment when applying to patients with extremes of risk (Appendix E3).

Evaluation and Review of Recommendations

Once drafted, the policy was distributed for internal review (by members of the entire committee) followed by external expert review and an open comment period for all ACEP membership. Comments were received during a 60-day open comment period with notices of the comment period sent electronically to ACEP members, published in *EM Today*, posted on the ACEP Web site, and sent to other pertinent physician organizations. The responses were used to further refine and enhance this clinical policy, although responses do not imply endorsement. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly.

Application of the Policy

This policy is not intended to be a complete manual on the evaluation and management of adult patients with seizure, but rather a focused examination of a critical question that has particular relevance to the current practice of emergency medicine. Potential benefits and harms of implementing recommendations are briefly summarized within the critical question.

It is the goal of the Clinical Policies Committee to provide evidence-based recommendations when the scientific literature provides sufficient quality information to inform recommendations for the critical question. In accordance with ACEP Resolution 56(21), ACEP clinical policies do not use race-based calculators in the formulation of recommendations. When the medical literature does not contain adequate empirical data to inform the critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to inform the critical question addressed in this policy. ACEP funded this clinical policy.

Scope of Application. This guideline is intended for physicians working in EDs.

Inclusion Criteria. This guideline is intended for adult patients aged 18 years and older presenting to the ED with generalized convulsive seizures.

Exclusion Criteria. This guideline is not intended for pediatric patients, pregnant patients, patients with complex partial seizures, patients with acute head trauma or multisystem trauma, patients with brain mass or brain tumor, immunocompromised patients, patients with eclampsia, or patients in the prehospital environment.

CRITICAL QUESTION

In emergency department patients with generalized convulsive status epilepticus who continue to have seizures despite receiving optimal dosing of benzodiazepine, which agent or agents should be administered next to terminate seizures?

Patient Management Recommendations

Level A recommendations. Emergency physicians should treat seizures refractory to appropriately dosed benzodiazepines with a second-line agent. Either fosphenytoin, levetiracetam, or valproate may be used with similar efficacy.

Level B recommendations. None specified.

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations:

- Reduced morbidity and mortality from undertreated seizures.

Potential Harm of Implementing the Recommendations:

- Adverse effects from fosphenytoin, levetiracetam, or valproate, including continued convulsions, altered level of consciousness, or respiratory distress.

Key words/phrases for literature searches: anticonvulsants, barbiturates, benzodiazepines, emergency medicine, epilepsy, hypnotics, ketamine, perampanel, recurrent status epilepticus, refractory status epilepticus, sedatives, seizures. status epilepticus and variations and combinations of the key words/phrases. Searches included January of 2011 to search dates of February 4, 5, 6, 7, and 8, 2022.

Study Selection: Nine hundred twelve articles were identified in the searches. Twenty-five were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, 1 Class I study, 1 Class II study, and 1 Class III study were included for this critical question (Appendix E4).

The 3 papers included in this review were composed of research from the Established Status Epilepticus Treatment Trial (ESETT) (clinicaltrials.gov, NCT01960075). ESETT was a double-blinded-comparative effectiveness trial that included patients aged 2 years and older who presented to an ED (57 academic, pediatric, and community hospitals across the United States) with ongoing convulsive seizures. To be included in the study, patients had to have been treated with an appropriate benzodiazepine (classified as diazepam 10 mg, lorazepam 4 mg, midazolam 10 mg, or a weight-based equivalent) for their seizures. A blinded comparison was made between levetiracetam (60 mg/kg), fosphenytoin (20 mg/kg), and valproate (40 mg/kg) as an anticonvulsant treatment for status epilepticus. The doses chosen were based on published experience in treating status epilepticus. The primary outcome was absence of clinically apparent seizure activity and an improvement in responsiveness at 60 minutes from infusion of treatment medication. No additional medications could be given, even if intubation medications were required. The seizure activity was defined by the treating emergency physician as any visual movements that were considered consistent with focal or generalized seizures. One limitation was the visual confirmation of seizure activity and not the use of electroencephalography.

The primary safety outcome was life-threatening hypotension or cardiac arrythmia occurring within the 60 minutes after start of medication infusion. Life-threatening hypotension required 2 consecutive readings of systolic pressure at least 10 minutes apart below age-specified thresholds. Endotracheal intubation was also recorded if required. Frequency of life-threatening hypotension was 0.7% in levetiracetam group, 3.2% in

fosphenytoin group, and 1.6% in valproate group. Arrythmias were only seen in 0.7% of the levetiracetam group. Endotracheal intubation occurred in 20% of levetiracetam group, 26.4% of the fosphenytoin group, and 16.8% of the valproate group. None of the safety outcomes were significantly different. The most frequent serious adverse events found in 42% of the subjects were continued convulsions, altered level of consciousness, and respiratory distress.

In a Class I study, Kapur et al published initial data from ESETT.[5] A total of 400 patient encounters were assessed for eligibility, enrolled, and underwent randomization. After excluding 16 patients for repeat enrollment in the intention-to-treat population, 384 unique patients were randomly assigned to 1 of 3 groups receiving IV levetiracetam (145), IV fosphenytoin (118), or IV valproate (121).[5] Patients aged 2 years and older were eligible for inclusion in the study. The primary outcome of cessation of status epilepticus and improvement in the level of consciousness at 60 minutes was reached in 68 patients who received levetiracetam (47%), 53 patients who received fosphenytoin (45%), and 56 patients who received valproate (46%). Secondary outcomes included time to termination of seizures, but this was only investigated in a subgroup where audio recordings were available to confirm the time of seizure cessation. Additional secondary outcomes were admission to the intensive care unit, length of intensive care unit stay, and overall length of hospital stay. Numerically more episodes of hypotension were present in the fosphenytoin group, but it was found not to be significant. The authors concluded that in benzodiazepine refractory status epilepticus, the use of the studied anticonvulsants led to cessation of seizures in about half of all patients with a similar incidence of adverse events no matter which medication was used.[5] Although this policy focused on adults, 39% of the ESETT subjects were pediatric (up to 17 years), subgroup analyses suggest findings may be relevant for adult and pediatric patients (ages included); but our search excluded pediatric patients so our recommendations are limited to adults.

In a Class II study, Chamberlain et al took the ESETT data and examined 3 age groups, <18 years, 18 to 65 years, and >65 years, to determine if age played a role in medication efficacy.[6] A total of 237 adult patients were included in this study, which accounted for just over half the study group. Adults 18 to 65 made up over 75% of the adults (N=186), and older adults (>65 years) made up just under the remaining 25% (N=51). The primary outcome was numerically found to be the greatest for adults (ages 18 to 65) in the fosphenytoin group at 46% (95% credible interval [CrI] 34 to 59), followed by the valproate group at 46% (95% CrI 34 to 58), and the

levetiracetam group at 44% (95% CrI 33 to 55). In older adults, greatest success was found in the valproate group at 47% (95% CrI 25 to 70), followed by levetiracetam group at 37% (95% CrI 19 to 59), and the fosphenytoin group at 35% (95% CrI 17 to 59). Secondary safety outcomes were similar across all the adult groups. No statistical difference was found between any age group with respect to the primary outcome. The authors concluded that among children, adults, and older adults, the cessation of seizures occurred again in roughly half of all patients receiving 1 of the 3 medications. These results were similar to the overall ESETT findings.[6]

In a Class III study using the ESETT data, Wabl et al investigated whether the use of the patient's home anticonvulsant medication as a second-line treatment for status epilepticus had an improved effect on seizure cessation.[7] In this preferred subgroup analysis, the patient's home medication lists were compared to the study drug given during their ED visit and checked whether they received a similar study medication.[7] Home medication concurrence was found if the patient took levetiracetam or brivaracetam at home and received study levetiracetam, or reported home use of phenytoin and received study fosphenytoin, or took valproate at home and received study valproate. Out of the 462 unique patients included in the study, a total of 232 (50%) were taking 1 to 2 of the 3 possible study medications used in ESETT.[7] The primary outcome was found in 39 of 89 patients (44%) who were randomized to their home medication group. In those randomized to a non-home medication group, the primary outcome was seen in 76 of 143 patients (53%). The authors concluded that for patients presenting to an ED with status epilepticus, the use of the home medication as a second-line agent did not affect probability of stopping the seizures.[7]

Summary

In the setting of benzodiazepine resistant status epilepticus, the use of levetiracetam, fosphenytoin, or valproate will result in cessation of seizures in approximately half of all patients. This outcome is not influenced by the patient's home medications or age. The benefit of early treatment and cessation of status epilepticus is a reduction in morbidity and mortality. The harms appear to be limited to the potential for an adverse drug reaction.

Future Research

Despite multiple previous studies investigating medications to abort status epilepticus, only the 3 included studies from the ESETT trial met methodologic inclusion criteria for this review. Additional studies on second-

line medications for status epilepticus are warranted. In addition, the ESETT studies only focused on outcomes at 60 minutes, further research on the longer-term outcomes or recurrence of status epilepticus during the initial 24 to 48 hours would be useful. Specific seizure etiologies are another area for possible investigation such as toxin, metabolic, or intracerebral hemorrhage related seizures. Although, the ESETT trial did a subgroup analysis of toxin-related seizures, there is not enough data to support recommendations for the treatment of status epilepticus secondary to toxins or alcohol withdrawal where fosphenytoin may not be effective.[8]

In addition, prospective areas of research in the treatment of status epilepticus should include additional medication therapies such as lacosamide, ketamine, propofol, and barbiturates.[9-11]

As previously suggested in the 2014 ACEP Clinical policy, research should also focus on accurately identifying convulsive seizures and non-convulsive status epilepticus. This research could focus on the use of electroencephalogram within the ED to better correctly identify these patients.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic.

Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical question.

REFERENCES

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Appendix E1. Literature classification schema.*

Design/ Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

Appendix E2. Approach to downgrading strength of evidence.

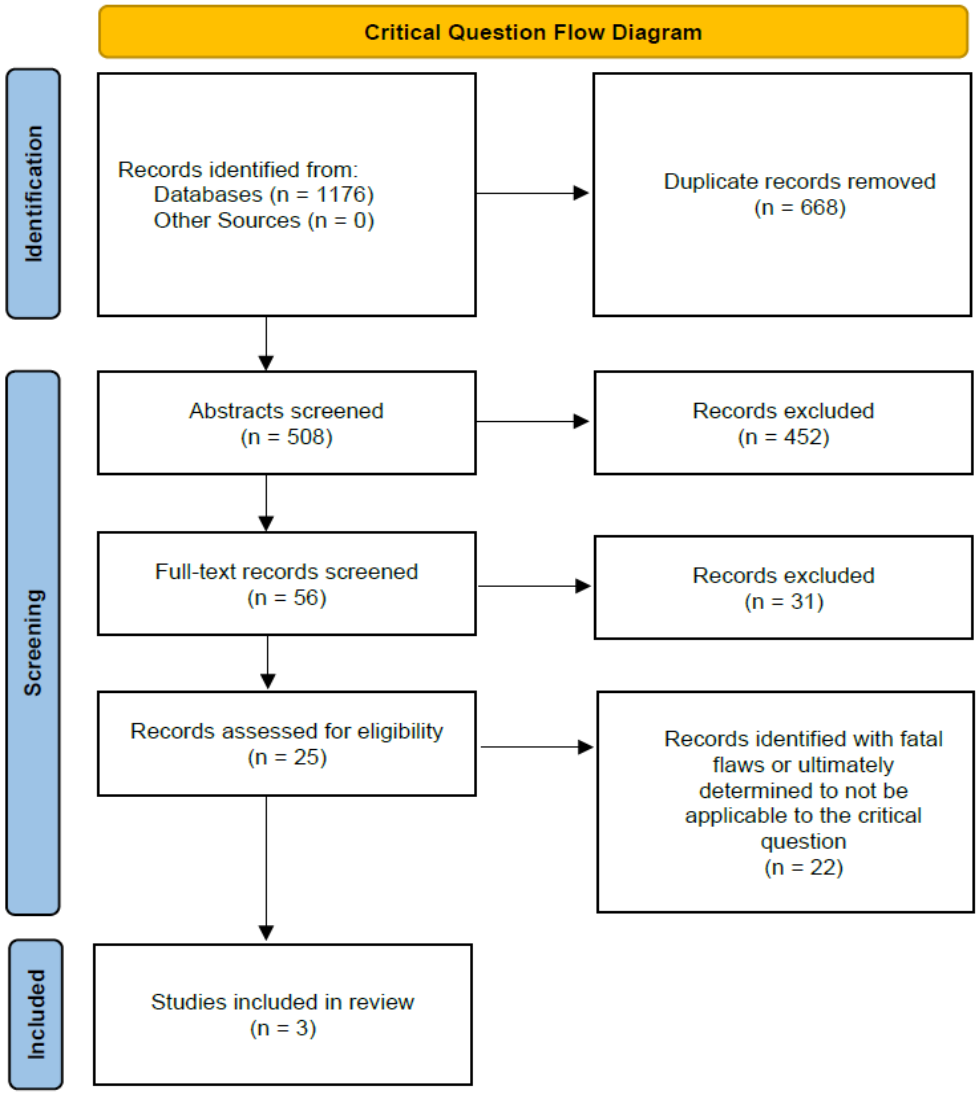
	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix E3. Likelihood ratios and number needed to treat.*

LR (+)	LR (–)	
1.0	1.0	Does not change pretest probability
1–5	0.5–1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Appendix E4. PRISMA[4] flow diagrams.



Evidentiary Table.

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Kapur et al[5] (2019)	I	ESETT trial; 57 hospital EDs across the United States, included academic, pediatric, and community hospitals; November 2015 to October 2017; double-blinded adaptive randomized clinical trial	Assessed comparative effectiveness of levetiracetam, fosphenytoin, and valproate given by IV infusion over 10 minutes for treatment of status epilepticus in the ED; primary outcome: absence of clinically apparent seizures and improved responsiveness 60 minutes after start of trial-drug infusion without additional anticonvulsant medication; secondary outcomes included time to seizure termination; patients were included if they were age 2 years and older, treated with accepted cumulative dose of benzodiazepines for generalized convulsive seizures >5 minutes, continued to have persistent or recurrent seizures after 5 to 30 minutes after the last dose of benzodiazepine; excluded major traumas, hypoglycemia, hyperglycemia, cardiac arrests, postanoxia; pregnancy, incarceration, wearing medical alert tag marked "ESETT declined", treated with alternative anticonvulsant agents prior to enrollment, intubation, allergies to any of the study medications	N=384; trial stopped early for futility to find a most effective or least effective treatment; Seizure improvement at <60 minutes: • levetiracetam 47% (95% CrI 39 to 55) • fosphenytoin 45% (95% CrI 36 to 54) • valproate 46% (95% CrI 38 to 55) Median time to seizure termination: • levetiracetam 10.5 minutes (IQR 5.7 to 15.5) • fosphenytoin 11.7 minutes (IQR 7.5 to 20.9) • valproate 7.0 minutes (IQR 4.6 to 14.9)	Limitations of this trial included need for unblinding in some instances in order to choose a second anticonvulsant to treat ongoing seizures (occurring after the determination of the primary outcome in most patients); 10% of the patients enrolled had psycho-genic nonepileptic seizures; 135 protocol violations but equally distributed among groups; clinical rather than electroencephalogram criteria used to determine the primary outcome of seizure cessation; was not possible to distinguish postictal or benzodiazepine-related sedation from continued non-convulsive status epilepticus as the cause of treatment failure in 52 patients who had resolution of clinically evident seizure without additional anticonvulsant medications but did not have improving consciousness at 60 minutes

365 **Evidentiary Table (continued).**

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcomes Measures	Results	Limitations and Comments
Chamberlain et al[6] (2020)	II	ESETT trial (see Kapur 2019 – original outcomes paper); enrollment continued to assess comparative effectiveness in children; November 2015 to December 2018	Primary outcome: absence of clinically apparent seizures and improved responsiveness 60 minutes after start of trial-drug infusion without additional anticonvulsant medication; secondary outcomes included time to seizure termination; primary safety outcome was a composite of life-threatening hypotension or life-threatening cardiac arrhythmia; secondary safety outcomes were need for endotracheal intubation within 60 minutes of the start of study drug infusion, acute seizure recurrence 60 minutes to 12 hours after the start of study drug infusion, acute respiratory depression at any time during the study period, and mortality	N=462; added 76 children and 2 adults to the enrollment from the original trail; 225 children, 186 adults, 51 older adults >65 years; no differential impact of study medications in total or stratified by age; seizure improvement <60 minutes: levetiracetam 47% (95% CrI 39 to 54), fosphenytoin 46% (95% CrI 38 to 55), valproate 49% (95% CrI 41 to 57); trend that children had higher response rates but not significant; no differential impact on safety outcomes aside for more intubations of children in the fosphenytoin group (33%) versus 8% in the levetiracetam and 11% in the valproate groups	See Kapur 2019; few older adults enrolled compared to children and adults 65 years and younger

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367 **Evidentiary Table (continued).**

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcomes Measures	Results	Limitations and Comments
Wabl et al[7] (2021)	III	Unplanned tertiary analysis of ESETT trial data (see Kapur 2019 – original outcomes paper and Chamberlain 2020 – outcomes age stratified)	Analyzed outcomes comparing patients who randomly received the same medication as what the patients are prescribed for seizure treatment/prophylaxis; sample restricted to patients who were taking either 1 or 2 study drugs at home	N=232 patients; 74% on levetiracetam only, 6% levetiracetam and phenytoin, 7% levetiracetam and valproate, 5% phenytoin only, 7% valproate only, and 1% phenytoin and valproate; among participants who were noncompliant with medications, those receiving concordant therapy trended towards improved outcomes; those who were compliant trended towards improved outcomes after receiving alternative therapies; the primary seizure cessation outcome occurred in 39 of 89 (44%, 95% CI 34% to 54%) patients treated with a home medication versus 76 of 143 (53%, 95% CI 45% to 61%) patients treated with a nonhome medication; among the 204 patients taking home levetiracetam, 27 of 72 (38%, 95% CI 26% to 49%) patients treated with study levetiracetam achieved seizure cessation, while 74 of 132 (56%, 95% CI 48% to 65%) patients treated with study fosphenytoin or valproate treatment achieved cessation; among patients not taking home levetiracetam, 55 of 103 (53%,	See comments for Kapur 2019 and Chamberlain 2020; few patients were home prescribed medications other than levetiracetam, limiting conclusions about the group in aggregate; patient compliance with seizure medications was self-reported

				95% CI 44% to 63%) patients treated with study levetiracetam cessation, while 73 of 155 (47%, 95% CI 39% to 55%) patients treated with study fosphenytoin or valproate achieved the secondary outcome; the interaction between study levetiracetam and home levetiracetam was significant (*P*= 0.01)	

368 *CI*, confidence interval; *CrI*, credible interval; *ED*, emergency department; *ESETT*, Established Status Epilepticus Treatment Trial; *IQR*, interquartile range.