



Effectiveness of Non-benzodiazepine Antiepileptic Drugs in Benzodiazepine-resistant Convulsive Status Epilepticus: A Review

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ABSTRACT

Time-dependent pharmacoresistance is a major therapeutic problem in SE and CSE. As seizures continue, pharmacoresistance develops progressively. The anti-seizure effectiveness of benzodiazepines could reduce 20-fold in 30 min of seizures. The objective of this study is to précis the existing proof that compares the effect of valproate, phenytoin, diazepam, phenobarbital, lacosamide, and levetiracetam on benzodiazepine-resistant convulsive status epilepticus. This systematic review was conducted, including PubMed, Google Scholar, and EBSCO that examining randomized trials of non-benzodiazepine antiepileptic drugs in benzodiazepine-resistant convulsive status epilepticus. Authors extracted the data, and then the author's names, year and region of publication, the study type, period of study, and the result were reported.

The review included 9 randomized studies that compared non-benzodiazepine antiepileptic drugs in terms of efficacy and adverse effects for SE management. Valproate, phenytoin, diazepam, phenobarbital, lacosamide, and levetiracetam are all conventional agents that could be given as second-line management of status epilepticus and in cases of benzodiazepine-resistant convulsive status epilepticus. Though, the use of these medications is restricted due to their toxicity.

Key Words: *Drugs, Non-benzodiazepine, Epilepticus, Antiepileptic*

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INTRODUCTION

Status epilepticus (SE) is still challenging although the good progress in epilepsy management. SE has 27% mortality and high morbidity as many SE patients end up with permanent brain damage [1, 2]. The incidence rate was reported to be 18.1/100,000 and represents approximately 6% of emergency department cases of seizures in the US [3, 4].

In the 19th century, SE liability was recognized to become self-sustaining and resistant to pharmacotherapy. Time-dependent pharmacoresistance is a major therapeutic problem in SE and CSE. As seizures continue, pharmacoresistance develops progressively. The anti-seizure effectiveness of benzodiazepines could reduce 20-fold in 30 min of seizures. Once seizures are self-sustaining, few agents are effective in terminating them, and they usually work only in large concentrations [5].

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Certain conservative agents being given as second-line treatment comprise phenytoin (PHT), fosphenytoin, and valproate. Though, using of these medications is restricted by their toxicity (lorazepam: hypotension and respiratory conquest; phenytoin: hypotension, purple glove syndrome, and cardiac toxicity) [6]. Consequently, there is a necessity for different, more specific, and less toxic medications for managing SE. Further, lately, levetiracetam (LEV) has similarly been credited to the management of SE nonetheless there is quite a deficiency of elegant clinical trials back up its effectiveness in SE [7].

Conventionally, IV phenytoin or phenobarbital in addition to other medications were given in benzodiazepine-resistant SE. Phenobarbital and phenytoin could lead to cardiac arrhythmias, lowering blood pressure, and respirational depression. Using these drugs depended on ritual and clinical practice more than the evidence. Recently, using IV preparations of added anti-epileptic medicines, like valproic acid (sodium valproic acid) in benzodiazepine-unaffected SE has become greater than before [8].

While choosing the best antiepileptic drugs for seizure controller, the pharmacokinetics of the interference need to be concerned. This comprises, for instance, the period of action besides the route of administration.

Some prescriptions have benefits regarding safety and enhanced tolerability, but accessibility and price might also remain a matter [9].

Aim of the study

To review the existing evidence that compares the effect of valproate, phenytoin, diazepam, phenobarbital, lacosamide, and levetiracetam on benzodiazepine-resistant convulsive status epilepticus.

MATERIALS AND METHODS

A systematic review was carried out, including PubMed, Google Scholar, and EBSCO using the following terms in different combinations: status epilepticus, valproate, phenytoin, diazepam, phenobarbital, lacosamide, and levetiracetam, benzodiazepine-resistant convulsive status epilepticus. we included all full texts [randomized controlled trials, observational, and experimental studies]. The authors extracted the data, and then the author's names, year and region of publication, the study type, period of study, and the result were reported (**Table 1**).

Statistical analysis

No software has been utilized to analyze the data. The data was extracted based on a specific form (**Figure 1**) that contains (Author's name, publication year, country, methodology, and results). These data were reviewed by the group members to determine the initial findings and the modalities of performing the surgical procedure. A twice review of every member's products was carried out to confirm the validity and reduce the errors.

RESULTS AND DISCUSSION

The search of the mentioned databases returned a total of 77 studies that were included for title screening. 67 of them were included for abstract screening, which led to the exclusion of 32 articles. The remaining 35 publications full-texts were reviewed. The full-text revision led to the exclusion of 26 studies, and 9 were enrolled for final data extraction (**Table 1**).

The involved studies had different study designs.

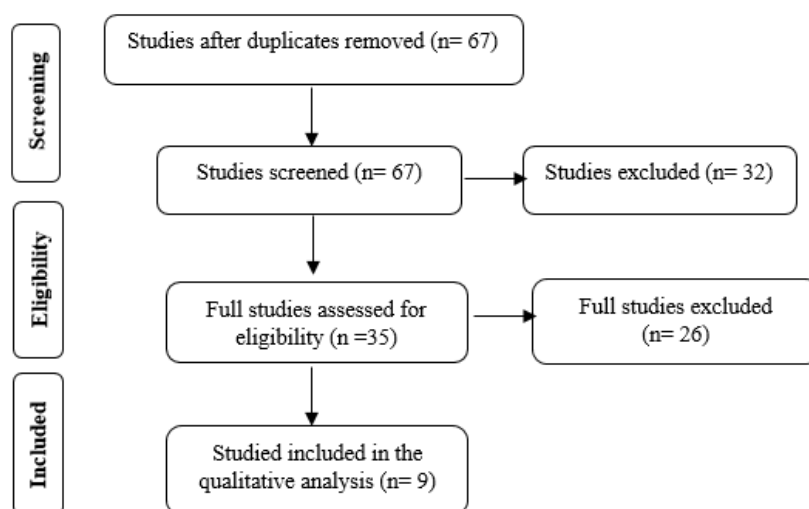


Figure 1. Flow chart representing the data extraction process

Y. Su *et al.* [10] included 73 cases in the study and reported that I.V phenobarbital was successful in 81.1% of cases, while I.V valproate was successful in 44.4% of cases ($p=0.05$). Number of opposing actions did not vary considerably in the 2 groups ($p [0.05]$). Neurological results of the phenobarbital group were better than those of the valproate group.

S. Chakravarthi *et al.* [11] reported that both LEV and PHT were similar in effect. PHT gained SE control in (68.2%) patients in comparison with LEV in (59.1%). Both groups reported similar results with regard to the recurrence of convulsions in 24 hours ($p=0.34$), discharge outcome as measured by functional independence test ($p=0.68$), requirement for respiratory assistance ($p=0.47$), and mortality ($p=1$).

Misra, *et al.* [12] included 66% with a median age of 40 (range 18-90) years. 24-hour seizure absence was inconsequentially greater in SVA (66.6%) compared with LCM (45.5%). Mortality (10 vs 12) and complex adverse effects (4 vs 6) were not meaningfully dissimilar in LCM and SVA individuals. LCM was linked with hypotension and bradycardia in one patient, besides SVA with liver cell failure in 6 cases.

Brigo, *et al.* [13] found that PHB was preferable to PHT, VPA, DZP, LEV, and LCM for SE cessation and scored higher than VPA, DZP, and LCM for 24-hour seizure

freedom. No discrepancies were observed between medications for respiratory depression and hypotension.

Sánchez Fernández, *et al.* [14] reported that phenobarbital was most effective non-BZD AED with a probability of SS of 0.8, followed by valproate, lacosamide, levetiracetam, and phenytoin/fosphenytoin.

Nalisetty, *et al.* [15] enrolled 61 children in the study and reported that (98%) of children required Pediatric Intensive Care Unit. A significant number of cases received extra anti-epileptic drugs in the fosphenytoin group (31%) compared to the levetiracetam group (7%) to control seizure.

Yasiry and Shorvon [16] reported that levetiracetam efficacy was 68.5%, phenobarbital 73.6%, phenytoin 50.2%, and valproate 75.7%.

Chen *et al.* [17] reported that in the DZP group, the seizure was controlled in 56% and 50% of the VPA group ($P=0.652$). In the VPA group, no patients developed respiratory depression, hypotension, nor hepatic dysfunction, while in the DZP group, 5.5% required ventilation and 5.5% developed hypotension.

Agarwal *et al.* [18] found that VVA was effective in 88% and IV phenytoin in 84% ($p>0.05$) of SE patients <2h ($p<0.05$). The overall number of adverse effects did not show any significant difference between the two groups ($p>0.05$).

Table 1. Author, year of publication, study type, and study outcome

Author	Year of publication	Country	Study type	Outcome	Ref
Su <i>et al.</i>	2016	China	A Prospective Randomized Controlled Trial	I.V phenobarbital seems to be more effective than IV valproate for GCSE adult patients.	[8]
Chakravarthi <i>et al.</i>	2015	India	Randomized trial	LEV is an effective alternative to PHT for SE management.	[9]
Misra, <i>et al.</i>	2017	India	A pilot study	LCM and SVA have almost similar efficacy and safety for the management of patients with LOR-resistant SE.	[10]
Brigo, <i>et al.</i>	2019	Italy	A systematic review and network meta-analysis	PHB in high doses is effective in SE management and seizure recurrence prevention. LCM and VPA may be better-tolerated alternatives.	[11]
Sánchez Fernández, <i>et al.</i>	2019	Spain	A systematic review and Meta-analysis	VPA and PB have higher efficacy for SE management than PHT. There is considerable overlap in the expense of non-BZD for SE management, however, the information provided does not assistance the pre-eminence of PHT, either for efficiency or price.	[12]
Nalisetty, S. <i>et al.</i>	2020	India	An open-label randomized controlled trial	Levetiracetam is an effective alternative to fosphenytoin for the management of BRSE in children.	[13]
Yasiry & Shorvon	2014	UK	A systematic review and Meta-analysis	The BRSE first-line management is Valproate, levetiracetam and phenobarbital. Phenytoin was not supported by evidences to be a first line treatment.	[14]
Chen, <i>et al.</i>	2011	China	A pilot study	IV VPA and DZP infusion are both beneficial second-line anticonvulsants for GCSE. IV VPA is	[15]

				well tolerated and no respiratory depression or hypotension was associated as in the DZP group.	
Agarwal <i>et al.</i>	2007	India	Randomized study	IV VA was found to be effective as IV phenytoin. IV VA is better tolerated and can be used in patients with cardio-respiratory disease as an alternative to phenytoin.	[16]

Phenytoin or fosphenytoin are considered second-line medications with the most use in the treatment of Yasiry & Shorvon [16] reported that phenytoin is not supported by evidence to be the first-line treatment. A previous uncontrolled trial recommended that 50% of cases not effectively cured with a benzodiazepine only may be improved by phenytoin [19].

Phenobarbital has a long half-life and significant cardiorespiratory depressant effects with similar dosing as phenytoin. Four non-controlled studies [20-23] varied in their study populations investigated the tolerance of IM phenobarbital and its prophylactic effects on seizure frequency reported no notable adverse effects, apart from a tendency of phenobarbital to deepen coma or render patients sleepy that was identified in the Kuile *et al.* (1992) [20] study or to experience respiratory depression as in Kokwaro *et al.* (2003) study [21].

Direct comparisons of intravenous phenobarbital and valproate were reported by Malamiri *et al.* [24] among children with convulsive SE (CSE) and acute prolonged convulsive seizures; higher doses or fast IV rate may result in higher blood-drug levels sooner, which may cause serious adverse events. IV phenobarbital was effective in 77 percent of patients as opposed to 90 percent of patients requiring IV valproate. There were few adverse reactions for phenobarbital, with a 3.3 percent hypoventilation and a 0 percent hypotension. Yasiry and Shorvon [16] reviewed eight studies describing treatment with IV valproic acid in 250 benzodiazepine-resistant episodes yielded a mean effect size for the efficacy of valproic acid of 75.7%.

Lacosamide (LCM) is a novel agent that has been developed as an antiepileptic drug. It is fractionalized amino-acid; its action is a discerning augmentation of sluggish sodium channel inhibition [25]. A meta-analysis constructed on 136 incidents of refractory SE discovered an overall desired effect in 56% and adverse effects in 25% [26].

A case-control study of SE and cluster convulsions found 86% of cases with SE and the cases of cluster convulsions completely improved on LCM (LCM was used as the first or second choice) [27].

Since 2008, Levetiracetam (LEV) is one of the newest AEDs. It is progressively more given for rapid control of convulsions and SE. However, as LEV is used for controlling SE, there is a scarcity of documents approving its role in SE and contrasts of its efficiency by the second-

line medications [11]. It was stated that LEV poses an advantage over fosphenytoin in its safety outline because of deficiency of opposing actions as cardiopulmonary depression and the nonexistence of any end-organ damage. There are numerous studies approving the excellence of levetiracetam for status epilepticus controlling in children and adult cases, however, scarce studies are present by comparator arm particularly in children and adolescents [28-31].

These adverse reactions require the managing of cases of SE in the Intensive Care Unit (ICU), having conveniences for mechanical ventilation in addition to cardiac monitoring, which might be needed [32]. Nalissetty, *et al.* [15] reported that (98%) of children prerequisite Pediatric ICU. In a previous study, a good treatment protocol was confirmed to be associated with better seizure control and even shorter intensive care unit (ICU) stay and hospital length of stay [33].

CONCLUSION

Valproate, phenytoin, diazepam, phenobarbital, lacosamide, and levetiracetam are all conventional agents that could be selected as second-line drugs in cases of status epilepticus and in cases of benzodiazepine-resistant convulsive status epilepticus. Though, giving these medications is restricted due to their toxicity. Randomized trials are recommended to compare the efficacy of these drugs. New, extra-effective, and nontoxic medications are needed for optimal management of SE.

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