# 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, 8].

Conventionally, IV phenytoin or phenobarbital in addition to other medications were given in benzodiazepine-resilient 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 [9].

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 [10, 11].

*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.



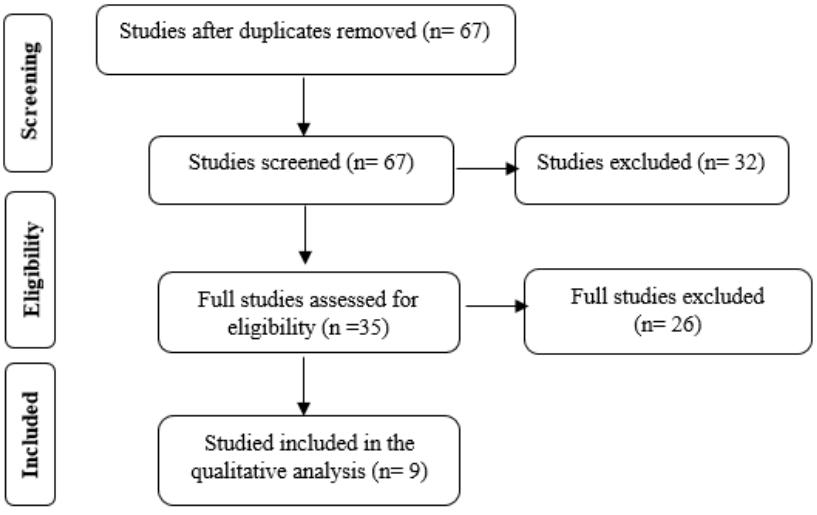


**Figure 1.** Flow chart representing the data extraction process

Y. Su *et al*. [12] 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*. [13] 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*. [14] 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*. [15] 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*. [16] 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*. [17] 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 [18, 19] reported that levetiracetam efficacy was 68.5%, phenobarbital 73.6%, phenytoin 50.2%, and valproate 75.7%.

Chen *et al*. [20] 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*. [21] found that VVA was effective in 88% and IV phenytoin in 84% (p>0.05) of SE patients with a slightly improved response in 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 *et al*. | 2016 | China | A Prospective Randomized Controlled Trial | I.V phenobarbital seems to be more effective than IV valproate for GCSE adult patients. | [9] |
| Chakravarthi *et al*. | 2015 | India | Randomized trial | LEV is an effective alternative to PHT for SE management. | [10] |
| Misra, *et al*. | 2017 | India | A pilot study | LCM and SVA have almost similar efficacy and safety for the management of patients with LOR-resistant SE. | [12] |
| Brigo, *et al*. | 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. | [13] |
| Sánchez Fernández, *et al*. | 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. | [14] |
| Nalisetty, S. *et al*. | 2020 | India | An open-label randomized controlled trial | Levetiracetam is an effective alternative to fosphenytoin for the management of BRSE in children. | [15] |
| 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. | [16] |
| Chen, *et al*. | 2011 | China | A pilot study | IV VPA and DZP infusion are both beneficial second-line anticonvulsants for GCSE. IV VPA is | [17] |

| | | | | | |
|---|---|---|---|---|---|
| | | | | well tolerated and no respiratory depression or hypotension was associated as in the DZP group. | |
| Agarwal *et al*. | 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. | [18] |

Phenytoin or fosphenytoin are considered second-line medications with the most use in the treatment of Yasiry & Shorvon [18] 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 [22, 23].

Phenobarbital has a long half-life and significant cardiorespiratory depressant effects with similar dosing as phenytoin. Four non-controlled studies [24-27] 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) [25] study or to experience respiratory depression as in Kokwaro *et al*. (2003) study [24, 28].

Direct comparisons of intravenous phenobarbital and valproate were reported by Malamiri *et al*. [29] 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 [18] 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 [30]. A meta-analysis constructed on 136 incidents of refractory SE discovered an overall desired effect in 56% and adverse effects in 25% [31].

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) [32].

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 [13]. 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 [33-38].

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 [39]. Nalisetty, *et al*. [17, 40] 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 [41].

## 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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## REFERENCES

[1] Niquet J, Baldwin R, Suchomelova L, Lumley L, Naylor D, Eavey R, et al. Benzodiazepine-refractory status epilepticus: pathophysiology and principles of treatment. Ann N Y Acad Sci. 2016;1378(1):166-73. doi:10.1111/nyas.13147

[2] Farrukh MJ, Bakry MM, Hatah E, Jan TH. Association between complementary and alternative medicines (CAM) usage and self-perceived cognitive impairment among epilepsy patients. Arch Pharma Pract. 2020;11(2):124-9.
[3] Knake S, Rosenow F, Vescovi M, Oertel WH, Mueller HH, Wirbatz A, et al. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia. 2001;42(6):714-8.
[4] Alyoubi RA, SB-Ped CS. Applying Experiential Learning Theory to Paediatric Post-Graduate Epilepsy Training. Int J Pharm Res Allied Sci. 2020,9(4):147-50.
[5] Kapur J, Macdonald RL. Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. J Neurosci. 1997;17(19):7532-40.
[6] O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of thepurple glove syndrome in patients receiving intravenous phenytoin. Neurology. 1998;51(4):1034-9.
[7] Alvarez V, Januel JM, Burnand B, Rossetti AO. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. Epilepsia. 2011;52(7):1292-6.
[8] Alhazmi K, Alghamdi S. Appendectomy and Parkinson's disease risk: a meta-analysis. World J Environ Biosci. 2021;10(1):19-23. doi:10.51847/zAvuw7jQXD
[9] Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16(1):48-61.
[10] Trinka E. What is the relative value of the standard anticonvulsants: phenytoin and fosphenytoin, phenobarbital, valproate, and levetiracetam?. Epilepsia. 2009;50:40-3. doi:10.1111/j.1528-1167.2009.02368.x
[11] Latysheva N, Ovchinnikov A, Okhotnikov I, Shvedov L, Yashkova N. Organizational behavior entities of engaged in the EAEU foreign economic activity. J Organ Behav Res. 2021;6(1):1-5. doi:10.51847/8lXuQmH2c2
[12] Su Y, Liu G, Tian F, Ren G, Jiang M, Chun B, et al. Phenobarbital Versus Valproate for Generalized Convulsive Status Epilepticus in Adults: A Prospective Randomized Controlled Trial in China. CNS Drugs. 2016;30(12):1201-7. doi:10.1007/s40263-016-0388-6
[13] Chakravarthi S, Goyal MK, Modi M, Bhalla A, Singh P. Levetiracetam versus phenytoin in management of status epilepticus. J Clin Neurosci. 2015;22(6):959-63. doi:10.1016/j.jocn.2014.12.013 0967-5868/Ó2015 Elsevier Ltd.
[14] Misra UK, Dubey D, Kalita J. Comparison of lacosamide versus sodium valproate in status epilepticus: a pilot study. Epilepsy Behav. 2017;76:110-3. doi:10.1016/j.yebeh.2017.07.005
[15] Brigo F, Del Giovane C, Nardone R, Trinka E, Lattanzi S. Intravenous antiepileptic drugs in adults with benzodiazepine-resistant convulsive status epilepticus: A systematic review and network meta-analysis. Epilepsy Behav. 2019;101(Pt B):106466. doi:10.1016/j.yebeh.2019.106466
[16] Sánchez Fernández I, Gaínza-Lein M, Lamb N, Loddenkemper T. Meta-analysis and cost-effectiveness of second-line antiepileptic drugs for status epilepticus. Neurology. 2019;92(20):e2339-e48. doi:10.1212/WNL.0000000000007503
[17] Nalisetty S, Kandasamy S, Sridharan B, Vijayakumar V, Sangaralingam T, Krishnamoorthi N. Clinical Effectiveness of Levetiracetam Compared to Fosphenytoin in the Treatment of Benzodiazepine Refractory Convulsive Status Epilepticus. Indian J Pediatr. 2020;87(7):512-9. doi:10.1007/s12098-020-03221-2
[18] Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. Seizure. 2014;23(3):167-74. doi:10.1016/j.seizure.2013.12.007
[19] Mediani HS, Nurhidayah I, Lusiani L, Panigoro R. Predicting factors impact to quality of life of school age Thalassemic children in Indonesia. J Adv Pharm Educ Res. 2021;11(1):81-5. doi:10.51847/65grcUX
[20] Chen WB, Gao R, Su YY, Zhao JW, Zhang YZ, Wang L, et al. Valproate versus diazepam for generalized convulsive status epilepticus: a pilot study. Eur J Neurol. 2011;18(12):1391-6. doi:10.1111/j.1468-1331.2011.03420.x
[21] Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. Seizure. 2007;16(6):527-32. doi:10.1016/j.seizure.2007.04.012
[22] Walker M. Status epilepticus: an evidence based guide. BMJ. 2005;331(7518):673-7.
[23] Alshehri HGH, Alanazi YM, Alharbi KAA, Nogali BW, Albalawi AM, Alharthi HS, et al. An overview on splenic trauma management approach: literature review. Int J Pharm Res Allied Sci. 2021;10(1):50-4. doi:10.51847/vosPG1JzpZ

[24] Kokwaro GO, Ogutu BR, Muchohi SN, Otieno GO, Newton CR. Pharmacokinetics and clinical effect of phenobarbital in children with severe falciparum malaria and convulsions. Br J Clin Pharmacol. 2003;56(4):453-7.
[25] Kuile F, Nosten F, Chongsuphajaisiddhi T, Holloway P, Maelankirri L, White NJ. Absorption of intramuscular phenobarbitone in children with severe falciparum malaria. Eur J Clin Pharmacol. 1992;42(1):107-10.
[26] Murri L, Arrigo A, Bonuccelli U, Rossi G, Parenti G. Phenobarbital in the prophylaxis of late posttraumatic seizures. Ital J Neurol Sci. 1992;13(9):755-60.
[27] Sternowsky HJ, Lagenstein I. Phenobarbital in febrile convulsions of children (author's transl). Dtsch Med Wochenschr (1946). 1981;106(2):49-51. [German].
[28] Begeç ÖA, Bahşi E. Evaluation of the clinical performance of different bulk-fill composites according to clinical evaluation criteria. Ann Dent Spec. 2021;9(1):53-61. doi:10.51847/jRo0pUvJrR
[29] Malamiri RA, Ghaempanah M, Khosroshahi N, Nikkhah A, Bavarian B, Ashrafi MR. Efficacy and safety of intravenous sodium valproate versus phenobarbital in controlling convulsive status epilepticus and acute prolonged convulsive seizures in children: a randomized trial. Eur J Paediatr Neurol. 2012;16(5):536-41.
[30] Beydoun A, D'Souza J, Hebert D, Doty P. Lacosamide: pharmacology, mechanisms of action and pooled efficacy and safety data in partial-onset seizures. Expert Rev Neurother. 2009;9(1):33-42.
[31] Trinka E, Dobesberger J. New treatment options in status epilepticus: a critical review on intravenous levetiracetam. Ther Adv Neurol Disord. 2009;2(2):79-91.
[32] Höfler J, Trinka E. Lacosamide as a new treatment option in status epilepticus. Epilepsia. 2013;54(3):393-404.
[33] Goraya JS, Khurana DS, Valencia I, Melvin JJ, Cruz M, Legido A, et al. Intravenous levetiracetam in children with epilepsy. Pediatr Neurol. 2008;38(3):177-80.
[34] Kirmani BF, Crisp ED, Kayani S, Rajab H. Role of intravenous levetiracetam in acute seizure management of children. Pediatr Neurol. 2009;41(1):37-9.
[35] Abend NS, Monk HM, Licht DJ, Dlugos DJ. Intravenous levetiracetam in critically ill children with status epilepticus or acute repetitive seizures. Pediatr Crit Care Med. 2009;10(4):505-10.
[36] Mandal S, Mondal SK, Chatterjee A. Intravenous levetiracetam in pediatric refractory status epilepticus. Int J Med Appl Sci. 2013;5(10):8-14.
[37] Noori M, Liu X. Studying workgroup emotional climate (WEC) in the knowledge-based companies of Iran. J Organ Behav Res. 2021;6(1):120-34. doi:10.51847/pMktpewnTQ
[38] Enwa FO, Jewo AO, Oyubu LO, Adjekuko CO, Effiong V. Incidence of vaginal ınfections among females of different age categories in delta state, Nigeria. Bull Pioneer Res Med Clin Sci. 2022;1(1):18-23. doi:10.51847/C1oahQ115n
[39] Thiéry G, Kovačević P, Štraus S, Vidović J, Iglica A, Festić E, et al. From Mechanıcal Ventılatıon to Intensıve Care Medıcıne: a Challenge for Bosnıa and Herzegovına. Bosn J Basic Med Sci. 2009;9(Suppl 1):S69-S76.
[40] Chanda C, Aluru RR. Anticuagulants: an overview of natural and synthetic therapeutic anticoagulants. J Biochem Technol. 2021;12(1):17-21. doi:10.51847/GRccY6BTJ6
[41] Aranda A, Foucart G, Ducassé JL, Grolleau S, McGonigal A, Valton L. Generalized convulsive status epilepticus management in adults: a cohort study with evaluation of professional practice. Epilepsia. 2010;51(10):2159-67