REVIEW ARTICLE

Comparative Efficacy and Safety of Second-Line Antiseizure Drugs for Pediatric Benzodiazepine-Refractory Status Epilepticus: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Pediatric status epilepticus (SE) is a time-critical emergency in which benzodiazepines are the first-line therapy. However, approximately 40% of cases persist despite adequate dosing, constituting benzodiazepine-refractory SE (BRSE) with a substantial mortality risk. **Objectives:** Given the divergent guideline recommendations and limited pediatric-specific evidence for second-line antiseizure drugs (ASDs), this study aimed to compare the efficacy and safety of second-line agents in children with BRSE using randomized controlled trial (RCT) data. **Methods:** A PROSPERO-registered systematic review and frequentist network meta-analysis (Preferred Reporting Items for Systematic reviews and Meta-Analyses/Cochrane-aligned) searched MEDLINE, EMBASE, and CENTRAL through March 31, 2022, including English-language peer-reviewed RCTs of patients aged 1 month–18 years with BRSE. The interventions included Fosphenytoin, Levetiracetam, Valproate, Midazolam, Phenobarbital, and Diazepam, with phenytoin as the common comparator. **Results:** The primary outcome was seizure cessation within 60 min, and the secondary outcomes were 24-h seizure freedom/seizure recurrence and in-hospital mortality due to adverse events. Thirteen RCTs (n = 2,282; 59.4% male) from emergency and critical care settings in seven countries were included; the risk of bias was low in 10 trials, with two high-risk studies. No ASD demonstrated statistically significant superiority for seizure control within 60 min; however, fosphenytoin showed the highest probability of benefit (P-score 0.71) amid substantial heterogeneity (I^2 = 80.2%) and

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no evidence of publication bias for the primary outcome. For seizure recurrence, no treatment was clearly superior, although Levetiracetam ranked highest (P-score 0.84) with marked heterogeneity (I^2 = 81.97%). Mortality did not differ significantly between the treatments; midazolam showed a non-significant trend toward a higher risk. **Conclusion:** Overall, fosphenytoin may be most favorable for rapid seizure termination and Levetiracetam for reducing recurrence; however, high heterogeneity, limited direct comparisons, and imprecision preclude the definitive selection of a single optimal second-line ASD, underscoring the need for large multicenter pediatric RCTs addressing dosing, safety, and longer-term outcomes.

Key words: Antiseizure drugs, benzodiazepine-refractory, network meta-analysis, Pediatric, randomized controlled trials, seizure cessation, status epilepticus

INTRODUCTION

Status epilepticus (SE) is a critical pediatric emergency that requires rapid seizure cessation. Benzodiazepines are the initial treatment for convulsive SE in children.[1,2] However, approximately 40% of SE cases persist despite adequate benzodiazepine doses, termed benzodiazepine-refractory SE (BRSE), with a 17% fatality rate.[3-6] Second-line antiepileptic drugs (AEDs) include Phenytoin, Fosphenytoin, Levetiracetam, and Phenobarbital.[5]

SE is classified as early SE (5–30 min), established SE (>30 min), or refractory SE (RSE), defined as seizures persisting despite two or three anticonvulsants. Guidelines recommend complete seizure control within 60 min.[7] The SE classification has evolved. In the prodromal phase (<5 min), it is uncertain whether the seizure will self-resolve or develop into SE.[5,7]

The Japanese Guidelines for Pediatric SE 2023 emphasize early benzodiazepine intervention, followed by phenytoin/fosphenytoin or phenobarbital for BRSE management.[7] Conversely, Western Guidelines from the International League Against Epilepsy (ILAE) recommend Levetiracetam, Valproate, and Phenytoin.[5,8]

Despite research and evolving strategies, no consensus exists on the management of BRSE in children. Most reviews have focused on adults, highlighting the need for pediatric-specific evidence. Present guidelines endorse benzodiazepines as first-line treatment, successfully stopping approximately 70% of seizures.[6] However, many cases remain refractory and require second-line therapy.

A systematic review and network meta-analysis (NMA) are needed to fill the pediatric BRSE management gap using high-quality randomized controlled trial (RCT) evidence. Previous reviews have focused on adults; therefore, our focus will be on pediatric trials to identify the most effective second-line AEDs. This systematic review and NMA evaluated the comparative efficacy and safety of second-line antiseizure drugs (ASD) in pediatric patients with BRSE.

METHODS

This NMA was registered with PROSPERO (ID: CRD42024618272). The review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines,[9,10] and Cochrane Handbook cohort design recommendations.[11]

Two independent authors conducted a comprehensive literature search up to March 31, 2022, using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. Our strategy combined MeSH and Emtree terms with free-text related to "Status epilepticus" and "Benzodiazepine-Resistant."

This NMA included only English RCTs from peer-reviewed journals that met the following criteria:

- Population (P): Pediatric patients aged 1 month–18 years with BRSE.
- Intervention (I): AEDs, such as Fosphenytoin, Levetiracetam, Valproate, Midazolam, Phenobarbital, and Diazepam.
- Comparison (C): Phenytoin as a common comparator.
- Outcomes (O): The primary outcome was seizure cessation within 60 min of treatment. The secondary outcomes included 24-h seizure freedom, mortality due to adverse events, and treatment effects.

No restrictions were imposed on the study setting or publication date. We excluded animal studies, non-randomized trials, observational research, *in vitro*/*in vivo* studies, duplicates, single-arm trials, reviews, books, and similar materials. Studies with incomplete data, conference abstracts, protocols, and letters were excluded.

The Rayyan Software platform (https://www.rayyan.ai/) was used for evaluation and selection.[12] Two independent reviewers screened the search results to identify relevant RCTs using Microsoft Excel (United States). Initially, titles and abstracts were evaluated against the eligibility criteria, followed by a full-text review for inclusion. Disagreements were resolved through discussion.

Data extraction was performed independently by four reviewers using a pre-designed sheet, tested, and refined through pilot extraction in Microsoft Excel (United States). The extracted data were categorized into: (1) Summary and baseline data, including study ID, design, country, setting, sample size, age, sex, condition, intervention, and comparator; and (2) outcome data, covering cessation of seizures within 60 min, seizure freedom for 24 h post-treatment, and mortality during hospitalization.

The methodological quality of the included RCTs was assessed using the Cochrane Risk of Bias (ROB) 2 tool (4), which evaluates five domains: (1) Randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) outcome measurement, and (5) selection of the reported result. Four independent reviewers classified the studies as having a "low risk," "some concerns," or "high risk" of bias for each domain, resolving disagreements through a third reviewer.

Publication bias was evaluated using a funnel plot when more than 10 studies were available for the outcomes of interest. Asymmetry indicated potential publication bias, which was further assessed using Egger's asymmetry test for confirmation.[13]

A NMA was conducted using a frequentist hierarchical model to estimate the comparative efficacy of the interventions. Categorical outcomes were analyzed using odds ratios (OR) and 95% confidence intervals (CI). Analysis was performed using R statistical software (v 4.4.2) with "netmeta" and "meta" packages (v 2.9.0). To ensure model validity, the consistency between direct and indirect evidence was assessed. Treatment rankings were determined using the surface under the cumulative ranking (SUCRA) curve, where higher SUCRA values indicated greater efficacy and fewer adverse events.

Heterogeneity was assessed using the Q-statistic within study designs and the I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity. Incoherence within the network model was further examined using between-study variance, a random-effects design-by-treatment interaction model, and node-splitting analysis to compare direct and indirect treatment effects. Statistical significance was set at $P < 0.05$, and the findings were presented as relative rankings and probability distributions for each outcome.

RESULTS

The systematic search identified 3,784 records from databases and 120 from registers, totaling 3,904 records. After removing 55 duplicates, 3,849 unique records were screened by title and abstract. Of these, 3,308 were excluded for not meeting the

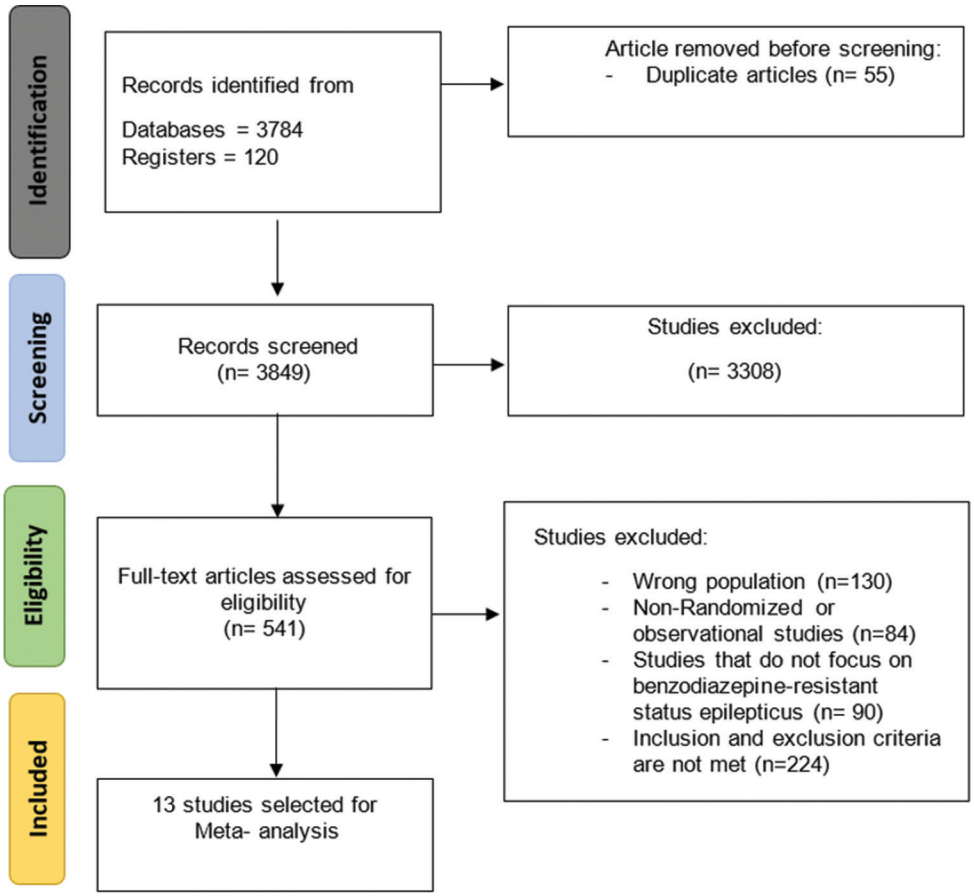


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study selection

inclusion criteria. The remaining 541 full-text articles were assessed for eligibility, and 528 were excluded. Ultimately, 13 RCTs were included in the analysis.[14-27] Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection process used in this review.

The 13 RCTs included 2,282 pediatric patients with BRES receiving various second-line AEDs, such as Phenobarbital, high-dose Levetiracetam, high-dose Valproate, Fosphenytoin, Phenytoin, and Midazolam.[14-27] The studies were conducted in countries, including India, the United States, the United Kingdom, Pakistan, Iran, Australia, and New Zealand, and were conducted in emergency units, ICUs, pediatric critical care units, and tertiary hospitals. Table 1 summarizes the trials.

The ages of pediatric patients ranged from 1 month to 18 years, covering infancy to adolescence. Males comprised 59.4% of the study population, while females comprised 40.6%, indicating a slight male predominance. Table 2 provides the baseline data of the patients.

The RoB 2 quality assessment found that 10 RCTs had low bias risk, while two studies had high risk, especially in randomization and result selection.[14,21] Despite "some

Table 1: Summary of included trials

Setting	No. of centers	Country	Study design	Study ID
Naeem *et al*., 2023	Open label, RCT	Pakistan	1	Paediatrics department
Chamberlain *et al*., 2020	Double-blind, response-adaptive, RCT	USA	58	Emergency units
Vignesh *et al*., 2020	Double-blind, RCT	India	1	Pediatric critical care
Nalisetty *et al*., 2020	Open-label, RCT	India	1	Tertiary care unit
Handral *et al*., 2020	RCT	India	N/M	Intensive care unit
Noureen *et al*., 2019	Open-label, RCT	Pakistan	1	Pediatric hospital
Lyttle *et al*., 2019	Open-label, RCT	UK	30	Emergency unit
Wani *et al*., 2019	Open-label, RCT	India	1	General hospital
Dalziel *et al*., 2019	Open-label, multicentre, RCT	Australia and New Zealand	13	Emergency units
Chakravarthi *et al*., 2015	Open label, RCT	India	1	Tertiary care unit
Malamiri *et al*., 2012	Single-blinded, RCT	Iran	2	Pediatric hospitals
Mehta *et al*., 2007	Open-label, RCT	India	1	Teaching hospital
Singhi *et al*., 2002	Open-label, RCT	India	1	ICU

RCT: Randomized controlled trial, N/M: Not mentioned, ICU: Intensive care unit

Table 2: Summary characteristics of included patients

Study ID	Total	Age	Gender (Lev group only) (%)	Condition	Intervention	Comparator
Naeem *et al*., 2023	134	1 yr–13 yrs	N/M	BRSE	Levtiracetam	Phenytoin
Chamberlain *et al*., 2020	462	6.1 yrs–42.6 yrs	Male=55 (Children)	BRSE	Levtiracetam	All drugs
Vignesh *et al*., 2020	102	3 yrs–12 yrs	N/M	CSE	Phenytoin	Phenytoin
Nalisetty *et al*., 2020	61	2 m–12 yrs	Male=53.1	BRSE	Fosphenytoin	Fosphenytoin
Handral *et al*., 2020	116	1 m–18 yrs	N/M	CSE	Levtiracetam	Fosphenytoin
Noureen *et al*., 2019	600	3.5±0.2 yrs	Male=72	BRSE	Levtiracetam	Phenytoin
Lyttle *et al*., 2019	286	6 m–<18 yrs	Male=49	BRSE	N/M	Phenytoin
Wani *et al*., 2019	104	1 m–12 yrs	Male=61.5	SE	Levtiracetam	Phenytoin
Dalziel *et al*., 2019	233	3 m–16 yrs	Male=48	CSE	Levtiracetam	Phenytoin
Chakravarthi *et al*., 2015	44	14 yrs–75 yrs	Male=56.8	SE	Phenytoin	Phenytoin
Malamiri *et al*., 2012	60	3 yrs–16 yrs	Male=45	CSE	Vaproate	Phenobarbital
Mehta *et al*., 2007	40	5 m–12 yrs	Male=77.5	RSE	Vaproate	Diazepam
Singhi *et al*., 2002	40	5 m–12 yrs	N/M	RSE	Midazolam	Diazepam

Lev: Levetiracetam, yrs: Years, m: Month, BRSE: Benzodiazepines refractory status epilepticus, CSE: Convulsive status epilepticus, SE: Status epilepticus, RSE: Refractory status epilepticus, N/M: Not mentioned, SE: Status epilepticus

concerns" regarding missing outcome data (D3) and outcome measurement (D4) in four other studies, the overall risk was low. Figure 2 presents a summary of the RoB 2 assessment.

Analysis of seizure control across different AEDs and doses (2,117 participants) showed no significant improvements with Fosphenytoin (OR = 0.72, 95% CI: 0.21–2.50, P-score = 0.71), Midazolam (OR = 1.08, 95% CI: 0.02–47.76, P-score = 0.51), Valproate (OR = 1.09, 95% CI: 0.21–5.60, P-score = 0.49), Levetiracetam (OR = 1.29, 95% CI: 0.61–2.71, P-score = 0.36), and Diazepam (OR = 1.54, 95% CI: 0.09–26.26, P-score = 0.38) compared to fosphenytoin [Figure 3]. These results suggest that no treatment was superior in terms of seizure control, with fosphenytoin showing a trend of effectiveness and the highest P-score. Diazepam had the lowest P-score (0.38) and highest OR (>1), indicating that it was the least effective.

However, the high heterogeneity (I^2 = 80.2%) suggests significant variability in treatment effects across studies, necessitating cautious interpretation, as the actual treatment effect may differ from the estimated one.

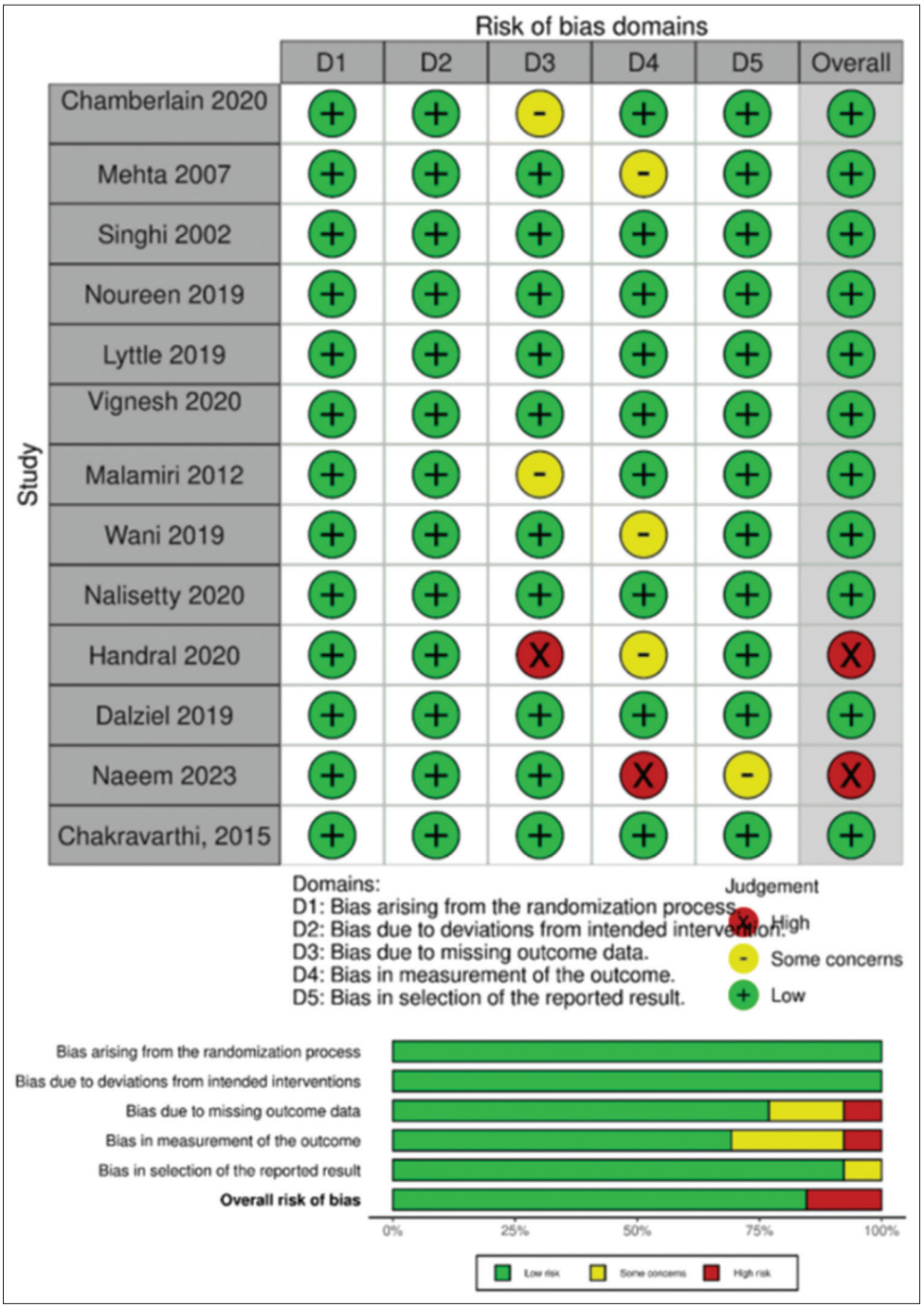
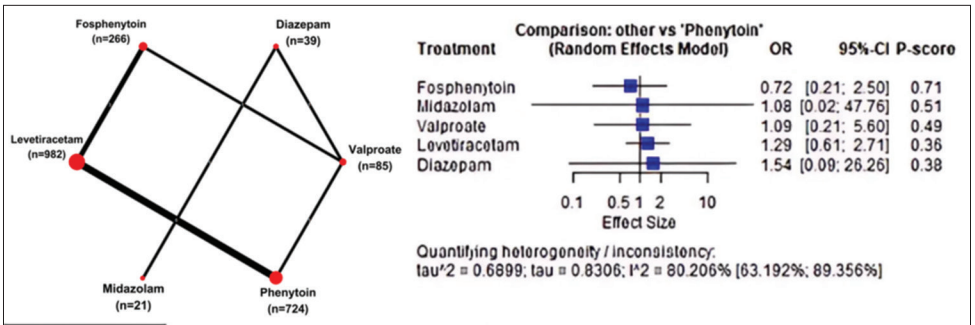


Figure 2: Quality assessment of the included studies using the risk of bias2



Diazepam					
2.15 [0.13; 36.99]	Fosphenytoin				
1.19 [0.07; 20.66]	0.55 [0.19; 1.62]	Levetiracetam			
1.42 [0.12; 17.48]	0.66 [0.01; 29.36]	1.19 [0.03; 53.14]	Midazolam		
1.54 [0.09; 26.26]	0.72 [0.21; 2.50]	1.29 [0.61; 2.71]	1.08 [0.02; 47.76]	Phenytoin	
1.42 [0.14; 14.34]	0.66 [0.13; 3.44]	1.19 [0.22; 6.27]	1.00 [0.03; 30.25]	0.92 [0.18; 4.74]	Valproate

Figure 3: Network geometry, forest plot, and league table for seizure control. OR: Odds ratio, CI: Confidence interval

Figure 4a shows the split plot of NMA comparing Fosphenytoin and Levetiracetam. Both direct and indirect evidence favored fosphenytoin, suggesting moderate heterogeneity (I^2 = 62%) with an estimate (OR = 0.55, 95% CI: 0.19–1.62), indicating that fosphenytoin may outperform Levetiracetam, although not significantly.

The comparison-adjusted funnel plots showed symmetry for the primary outcome, indicating no publication bias [Figure 4b].

The evaluation of seizure recurrence among 458 participants revealed that Levetiracetam (OR = 0.84, 95% CI: 0.01–1.80, P-score = 0.84), Valproate (OR = 0.16, 95% CI: 0.00–16.72, P-score = 0.70), Fosphenytoin (P-score = 0.40), and Midazolam (P-score = 0.17) did not show significant improvements compared to Phenytoin [Figure 5]. The results indicated that none of the treatments were superior in reducing seizure recurrence, although Levetiracetam showed a trend toward effectiveness with the highest P-score, followed by valproate. Midazolam, with the lowest P-score and the highest OR (>1), was the least effective. Figure 6 shows the split plot of the NMA for seizure recurrence. A high level of heterogeneity (I^2 = 81.97%) was observed, indicating considerable variability in treatment effects across different studies.

In terms of mortality, analysis from the three included studies found no significant differences with Levetiracetam (OR = 0.85, 95% CI: 0.10–7.04, P-score = 0.73) and Midazolam (OR = 5.22, 95% CI: 0.85–32.23, P-score = 0.07) compared to Phenytoin [Figure 7]. These findings suggest that no treatment was superior in terms of seizure recurrence, with Levetiracetam showing a trend of effectiveness due to its highest P-score. Figure 8 presents a split plot of the NMA for mortality.

Figures 9 and 10 show no evidence of publication bias among the studies included in the NMA. However, the funnel plot of Seizure Control showed the presence of outliers attributed to heterogeneity.

DISCUSSION

This NMA compiled data from 13 RCTs involving 2,282 pediatric patients with BRSE. We evaluated various ASDs using phenytoin as the primary comparator. Fosphenytoin had the highest likelihood of controlling seizures within 60 min (OR = 0.72, P-score = 0.71), whereas high-dose Levetiracetam was the most effective in minimizing seizure recurrence (OR = 0.84, P-score = 0.84). No medication showed statistically significant superiority in efficacy outcomes, with high heterogeneity (I^2 > 80%). Mortality rates were consistent across treatments, although midazolam presented the highest risk without statistical significance.

RSE is characterized by prolonged seizures that persist despite initial emergency interventions. The ILAE defines it as a seizure lasting 30–60 min that does not cease after first-line (benzodiazepines) and second-line treatments.[5] However, the 2023 Japanese guidelines for pediatric SE treatment deem

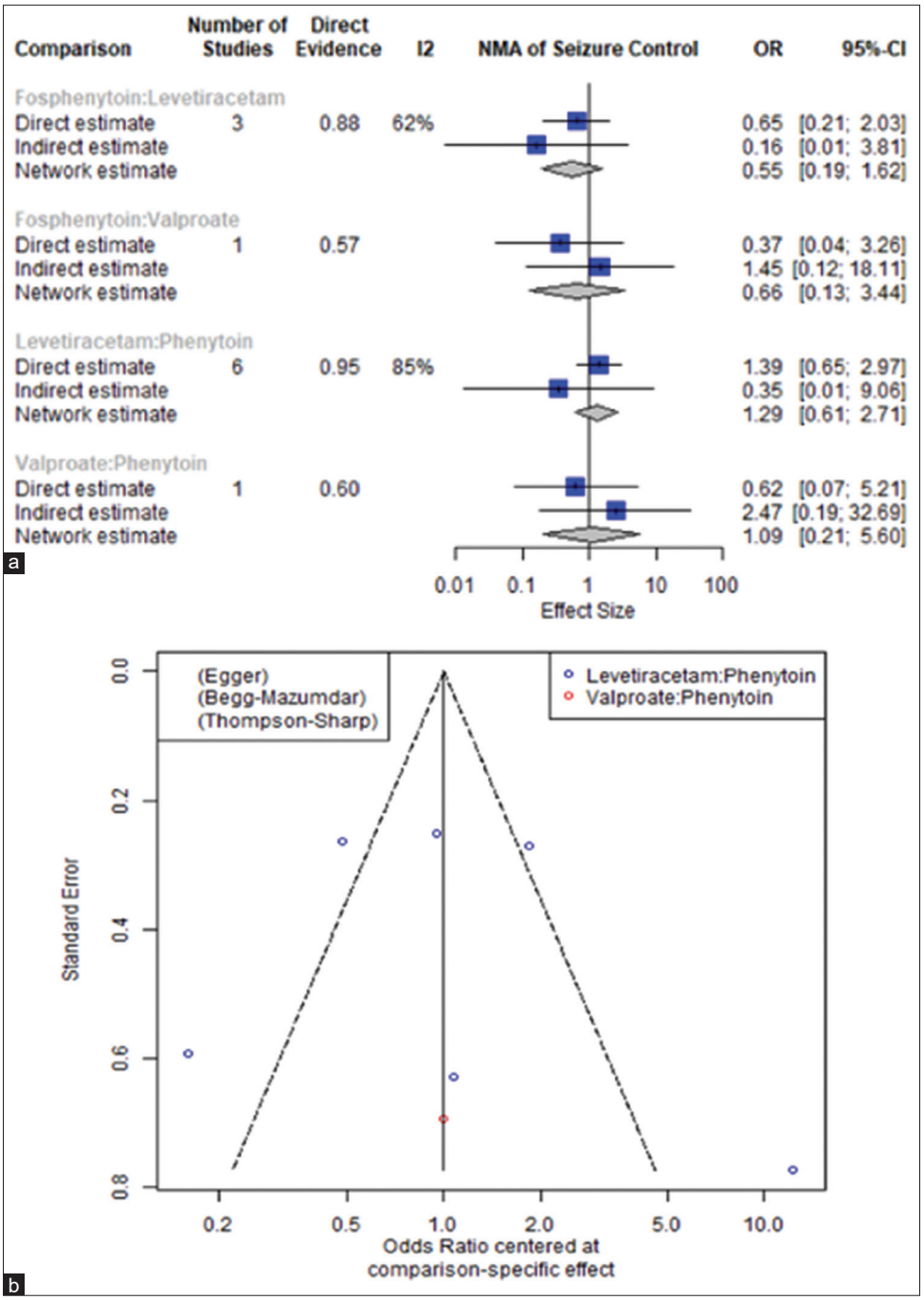


Figure 4: (a) Split plots and (b) Funnel plot for seizure control. OR: Odds ratio, CI: Confidence interval

it refractory if it continues beyond 60 min.[7] At this juncture, third-line treatment becomes essential.[5,7]

Conversely, BRSE in children is identified by drug responsiveness, with seizures continuing after two suitable doses of benzodiazepines (lorazepam or diazepam).[27] SE is more prevalent in children under 5 years old, with many resistant to first-line benzodiazepine therapy.[28] It can result from factors, such as febrile seizures, infections (encephalitis or meningitis), metabolic imbalances, and underlying epilepsy. If uncontrolled, it may lead to permanent brain damage.[7]

Understanding the pathophysiology of brain damage can elucidate the causes of RSE and BRSE. Within 30 min of seizure onset, physiological changes occur, including elevated blood pressure, hypercarbia, hypoxemia, and hyperthermia.[29] Prolonged seizures induce significant metabolic and physiological changes. Initially, the brain's oxygen consumption increases by 300%, and blood flow

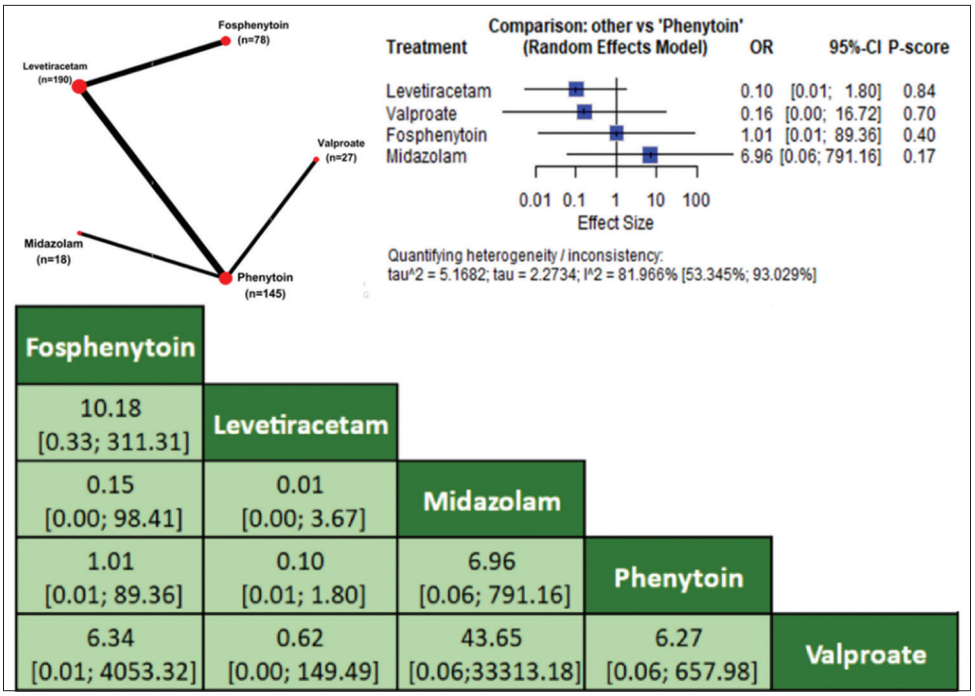


Figure 5: Network geometry, forest plot, and league table for seizure reoccurrence. OR: odds ratio, CI: Confidence interval

rises by 900% to meet its high energy demands, creating an energy compensatory state. After 60 min, the brain transitions into a severe phase known as an energy depletive state.[30] These prolonged seizures disrupt neurotransmitter receptor function. During extended seizures, gamma-aminobutyric acid_A receptors are internalized, weakening inhibitory signaling.[31,32] Simultaneously, N-methyl-D-aspartate receptors proliferate, heightening excitatory activity.[33] AMPA receptors remain highly adaptable, further sustaining seizure activity and reducing the effectiveness of benzodiazepines.[34,35]

Previous NMA have evaluated different ASDs in individuals with BRSE. In a meta-analysis of 17 RCTs, Jain *et al*. concluded that phenobarbital was the most effective in halting seizures within 60 min, followed by high doses of Levetiracetam and valproate. However, these results were constrained by significant heterogeneity.[36] Xue *et al*. found Levetiracetam was superior to phenytoin in seizure control and safety.[37] Both studies included pediatric and adult populations, potentially leading to different treatment responses. In addition, Brigo *et al*. noted that phenobarbital was most effective in adults, whereas lacosamide and valproate had better safety profiles. No single drug was consistently superior across all studies, suggesting the need for personalized treatment based on patient-specific factors.[38]

Fosphenytoin showed the highest probability of seizure control at 60 min (OR = 0.72, P-score = 0.71), yet no AED achieved statistical significance for efficacy. Consequently, although fosphenytoin ranked highest in probability, there was no clear second-line agent preference owing to wide CIs and high heterogeneity ($I^2 > 80\%$) at the time of analysis. These findings are consistent with Handral *et al*., who reported similar seizure cessation rates for fosphenytoin (93.1%) and Levetiracetam (91.4%), but with more cardiovascular side effects in the fosphenytoin group.[21]

Importantly, the Japanese guidelines by Kikuchi *et al*. recommended phenytoin/fosphenytoin and phenobarbital as second-line treatments for convulsive pediatric SE when benzodiazepines fail.[7] Jain *et al*. also supported phenobarbital's efficacy, demonstrating it was significantly more effective than phenytoin in children for seizure control, albeit based on low-quality evidence.[36]

Despite statistical uncertainty, individual studies have indicated a lower recurrence rate with Levetiracetam. Wani *et al*. observed that seizure recurrence between 1 and 24 h was significantly lower in the Levetiracetam group (3.8%) compared to the phenytoin group (34.6%).[23] Similarly, Naeem *et al*. reported no seizure recurrence within 24 h in the Levetiracetam group, whereas 16.4% of patients treated with phenytoin experienced recurrence.[14]

Chamberlain *et al*. found Levetiracetam, fosphenytoin, and valproate equally effective in stopping SE within 1 h, with response rates around 50%, and no single drug emerged as the best.[15] Similarly, Nalisetty *et al*. suggested that while Levetiracetam is a viable alternative to fosphenytoin, fewer

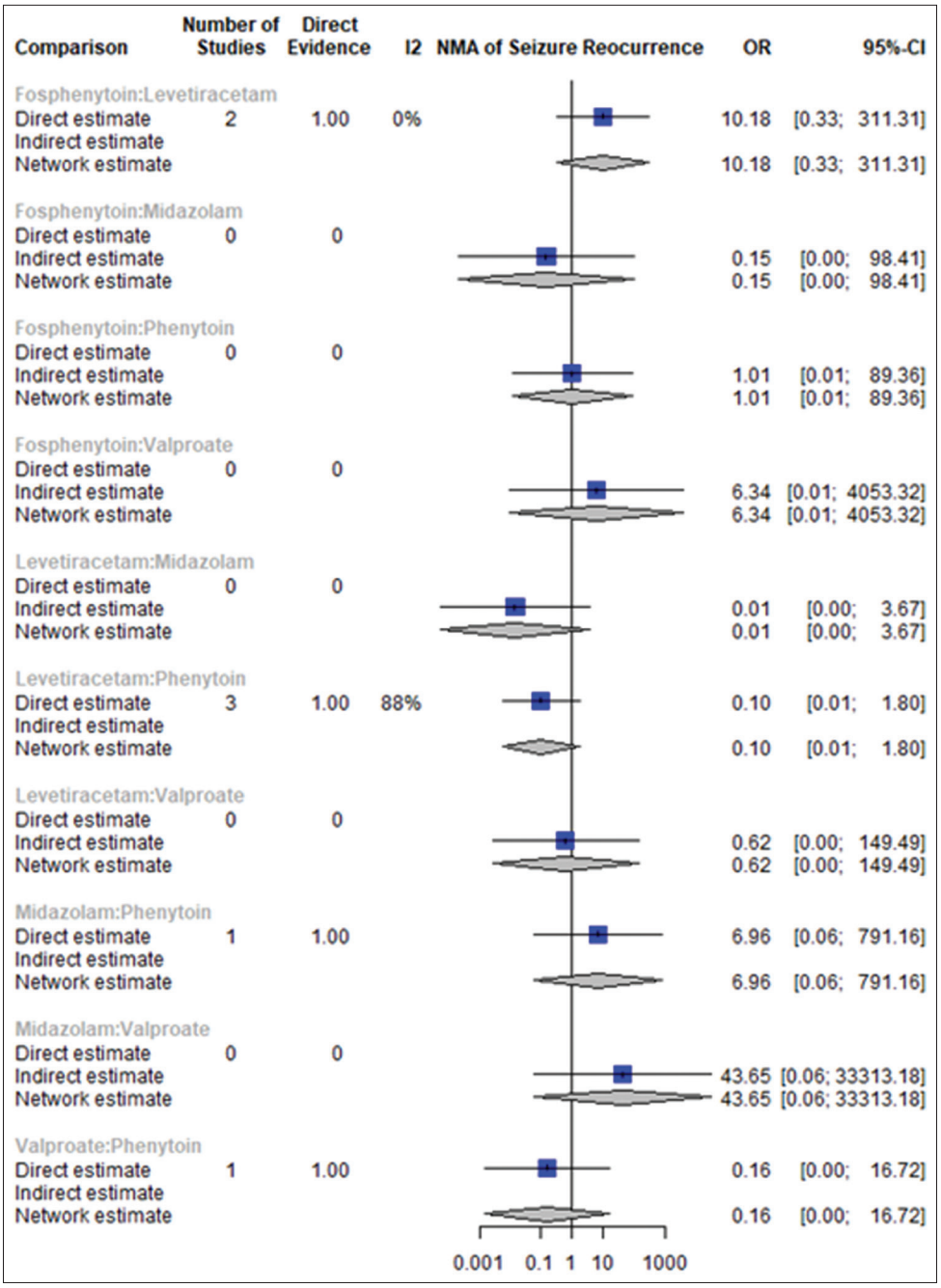


Figure 6: The split plot of network meta-analysis for seizure recurrence

patients treated with fosphenytoin required additional medications to manage their seizures.[20]

Our examination revealed that Midazolam (OR = 5.22) posed the greatest mortality risk compared to Phenytoin, while Levetiracetam (OR = 0.85) had a slightly reduced risk. However, none of the treatments were statistically significant. Previous research has shown similar patterns. Singhi *et al*. identified a higher mortality rate in the Midazolam group (38%) compared to Diazepam (10.5%), indicating possible safety issues.[18] Conversely, Naeem *et al*. and Noureen *et al*. reported no fatalities in the Levetiracetam or Phenytoin groups, highlighting their robust safety profiles.[14,25] In addition, two recent meta-analyses by Jain *et al*. and Zhang *et al*. demonstrated Levetiracetam had a superior safety profile compared to Fosphenytoin concerning respiratory depression rates and the necessity for intubation.[36,39]

Chamberlain *et al*. verified no significant mortality differences among Levetiracetam, Fosphenytoin, and Valproate.[15] These results imply Levetiracetam and Phenytoin remain

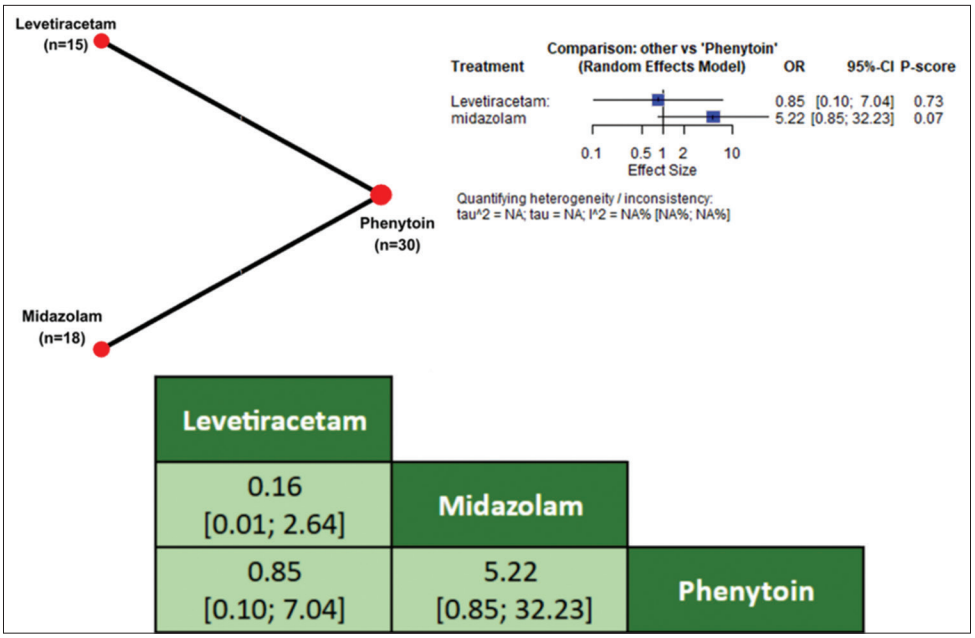


Figure 7: Network geometry, forest plot, and league table for mortality. OR: Odds ratio, CI: Confidence interval

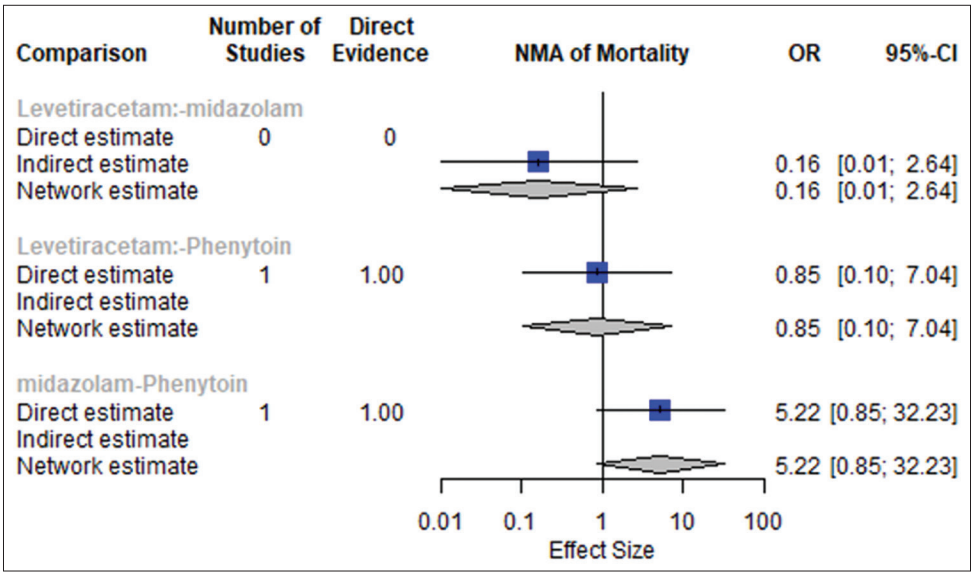


Figure 8: The split plot of network meta-analysis for mortality

safer choices, while further research is needed to evaluate Midazolam's potential risks in RSE.

The speed of administration is an important consideration. Levetiracetam, Fosphenytoin, and Valproate can be administered within 10 min, whereas Phenytoin and Phenobarbital require 20 min for infusion. Given the urgency in managing SE, Levetiracetam and Valproate offer benefits in terms of rapid administration.[39-41]

Limitations

This NMA faced several limitations: (i) Significant heterogeneity ($I^2 > 80\%$) in efficacy outcomes, likely due to variations in study populations, drug dosages, and treatment protocols, (ii) The generalizability of the findings is also limited by the small sample sizes in some intervention arms and studies conducted at single centers, (iii) The lack of direct evidence for certain ASDs results in less robust treatment ranking, (iv) Genetic differences among populations may contribute to varying drug responses and adverse effects, (v) The absence of sufficient long-term safety data and biomarkers for severe adverse effects hinders the personalization of treatment strategies, and (vi) The broad age range from neonates to adolescents is a limitation, as no age-specific analysis was performed, leaving the impact of age on effectiveness unclear.

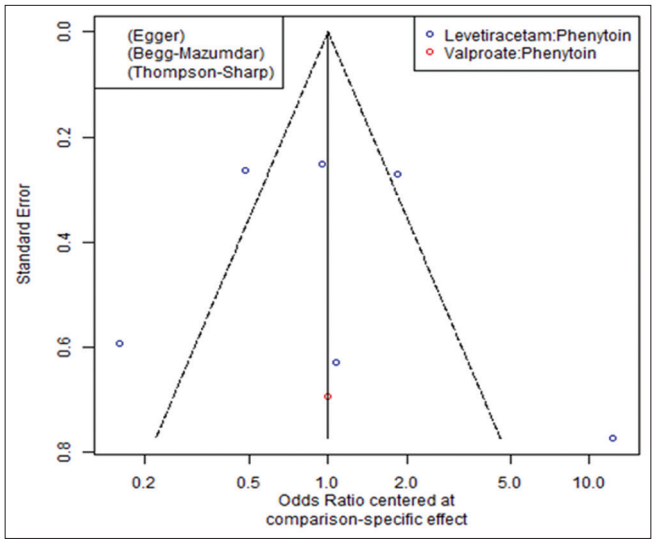


Figure 9: Comparison-adjusted funnel plot for seizure recurrence

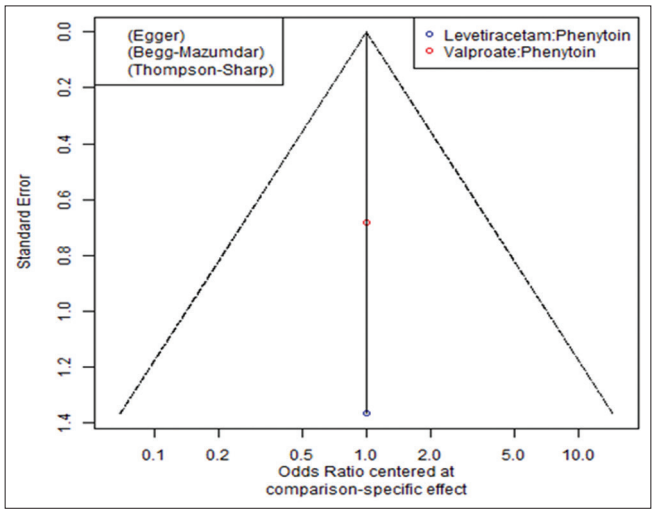


Figure 10: Comparison-adjusted funnel plot for mortality

CONCLUSION

Our findings indicate that fosphenytoin may be the most effective drug for stopping seizures, whereas Levetiracetam seems more suitable for preventing recurrence. However, no single drug showed a clear superiority. Mortality rates were similar, but high heterogeneity and limited direct comparisons prevented definitive conclusions. Future large-scale multicenter RCTs are necessary to determine the best ASD options, dosing strategies, and long-term safety.

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Not applicable.

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