Clinical Drug Investigation (2021) 41:1–17
https://doi.org/10.1007/s40261-020-00975-7

SYSTEMATIC REVIEW

Preferential Antiseizure Medications in Pediatric Patients with Convulsive Status Epilepticus: A Systematic Review and Network Meta-Analysis

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Accepted: 27 September 2020 / Published online: 4 November 2020

Abstract

Background and Objective The optimal choice for first- and second-line antiseizure medications for pediatric patients with convulsive status epilepticus remains ambiguous. The present study aimed to estimate the comparative effect on the efficacy and safety of different antiseizure medications in pediatric patients with status epilepticus and provide evidence for clinical practice.

Methods We searched PubMed, EMBASE, and the Cochrane Library for eligible randomized controlled trials. Inclusion criteria included: (1) pediatric patients; (2) diagnosis of status epilepticus; and (3) randomized controlled trials. Exclusion criteria were: (1) mixed population without a pediatric subgroup analysis; (2) not status epilepticus; (3) received the study drug prior to admission; (4) sample size fewer than 30; and (5) not randomized controlled trials. Primary outcome was seizure cessation. Secondary outcomes were seizure recurrence within 24 h, respiratory depression, and admission to an intensive care unit. The hierarchy of competing antiseizure medications was presented using the surface under the cumulative ranking curve.

Results Eight first-line antiseizure medication studies involving 1686 participants and eight second-line antiseizure medication studies involving 1711 participants were eligible for analysis. Midazolam, diazepam, lorazepam, and paraldehyde were administered as first-line antiseizure medications. Valproate, phenobarbital, phenytoin, fosphenytoin, and levetiracetam were investigated as second-line antiseizure medications. No significant differences were observed across first- and second-line antiseizure medications. Midazolam ranked the best for primary and secondary outcomes among the first-line antiseizure medications. Phenobarbital ranked the best for seizure cessation and a lower risk of admission to the intensive care unit. Valproate had superiority in preventing recurrence within 24 h. Levetiracetam had the lowest probability of developing respiratory depression.

Conclusions This study demonstrated the hierarchy of competing interventions. Midazolam could be a better option for first-line treatment. Phenobarbital, levetiracetam, and valproate had their respective superiority in the second-line intervention. This study may provide useful information for clinical decision making under different circumstances.

1 Introduction

Status epilepticus (SE) is one of the most common pediatric neurological emergencies. The incidence of pediatric SE is 3–42 episodes per 100,000 population per year [1]. Failure of SE cessation could cause irreversible neuronal

Yihao Zhang and Yingjie Liu contributed to this manuscript equally.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40261-020-00975-7) contains supplementary material, which is available to authorized users.

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Key Points

This network meta-analysis revealed the hierarchy of preferential antiseizure medications in first- and second-line treatment and provided useful information for clinical decision making.

We found midazolam could be a better option as a first-line antiseizure medication, while phenobarbital, valproate, and levetiracetam showed their respective advantages in efficacy and safety as second-line treatments.

injury and complications related to consequent changes in the neuronal network [2]. Therefore, it is vitally important to receive intervention as early as possible to terminate SE. Following the American Epilepsy Society (AES) guideline, benzodiazepines were commonly used as first-line antiseizure medications (ASMs), while paraldehyde was an alternative option [3]. In approximately one third of cases, SE cannot be terminated by a first-line intervention and required additional anticonvulsants. Valproate, phenobarbital, phenytoin, fosphenytoin, and levetiracetam are commonly used for second-line treatment. However, no evidence supported the most efficacious ASM as a second-line intervention for pediatric convulsive SE (CSE).

So far, the evidence of optimal ASMs for pediatric patients with CSE remains limited because of the small sample sizes and paucity of high-quality studies. To estimate the comparative effect on the efficacy and safety of different ASMs in eligible randomized controlled trials (RCTs) and provide hierarchical evidence on first- and second-line drug selection, we performed this network meta-analysis.

2 Methods

2.1 Search Strategy

We searched PubMed, EMBASE, and the Cochrane Library for any available study up to 20 May, 2020. Terms "status epilepticus", "prolonged seizure", "antiepileptic drug", "anticonvulsant", "randomized clinical trial", and "random" were searched in "title/abstract" and "Mesh term" or "Emtree" if available. There was no limitation in language or publication date. Details of the search strategy are reported in Appendix S1 of the Electronic Supplementary Material (ESM). A prespecified protocol registration has been submitted to PROSPERO (https://www.crd.york.ac.uk/prospero/) for review prior to the initiation of this study (registration number: CRD42020184940).

2.2 Selection Criteria

Inclusion criteria included: (1) pediatric patients (age: 1 month to 18 years); (2) patients diagnosed with CSE with a single convulsive seizure that lasted for at least 5 min, two or more sequential seizures without recovery of consciousness, or three or more sequential seizures [4]; and (3) randomized controlled trials (RCTs). The following studies were excluded: (1) mixed population (pediatric and adult) without an age group analysis; (2) studies with participants who did not meet the definition of CSE; (3) participants who received the study drug prior to admission; (4) a sample size fewer than 30; and (5) study design that was not randomized and controlled. Any disagreement was discussed within the group and evaluated by a third reviewer to reach a final consensus.

2.3 Data Extraction

Two independent reviewers (YZ and YL) screened articles by reading titles and abstracts. Full texts were further assessed for the eligibility. The following information was extracted: authors, publication year, country, study design, patient characteristics, etiology of seizures, intervention, dosage, route, sample size, primary outcome, and secondary outcomes. Primary outcome was defined as seizure cessation after drug infusion. Secondary outcomes included seizure recurrence within 24 h, patient admission to an intensive care unit (ICU), and respiratory depression. Modified intention-to-treat population data are preferred for data analysis. The modified intention to treat population is a subset of the intention-to-treat population, which allows exclusion of participants under justified conditions. The intention-to-treat population may include participants who never receive an intervention or are ineligible after randomization, which could be problematic especially in non-inferiority trials [5]. Therefore, the modified intention-to-treat population is appropriate for data synthesis.

Study quality was evaluated by Cochrane's Risk-of-Bias Tool 2 (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result) [6]. Any disagreement was discussed within the group and evaluated by a third reviewer to reach a final consensus.

2.4 Data Analysis

We performed a network meta-analysis within a Bayesian framework to directly and indirectly compare the efficacy and safety of different first- and second-line ASMs. The number of chains in our model was four. Considering that

seizure cessation and seizure recurrence were dichotomous data, we used binomial and logit values for likelihood and links function with a random-effect model and reported our data as odds ratios and 95% credible intervals for mixed comparisons or 95% confidence intervals (CIs) for direct comparisons. Convergence of the model was assessed after 10,000 iteration adaptations with a thinning factor of ten, and 50,000 iteration simulations to estimate the effect. Because event occurrence was relatively low for respiratory depression and admission to the ICU, the risk difference was calculated to estimate the effect size [7]. We assessed inconsistency between direct and indirect comparisons in the network using a nodesplit approach. A p value larger than 0.05 was considered as no inconsistency, hence a consistency model was used if eligible. Heterogeneity was evaluated using the I^2 test and p value. A p value less than 0.05 was considered of significant heterogeneity. Cumulative probability of efficacy and safety was presented as a surface under the cumulative ranking curve or a stacked column graph.

For the above-mentioned data analysis and image synthesis, we used freely available R packages GeMTC (https://CRAN.R-project.org/package=gemtc), pcnetmeta (https://cran.r-project.org/web/packages/pcnetmeta/index.html), and ggplot2 (https://cloud.r-project.org/package=ggplot2).

3 Results

3.1 Study Characteristics

We identified 1286 articles from PubMed, EMBASE, and the Cochrane Library. An additional review of references identified another five articles. Sixteen RCTs involving 3397 pediatric participants were included in the data analysis [8–23] (Fig. 1). The definition of CSE was homogenous between studies. Etiology of included studies varied remarkably across studies. The following drugs were included for comparison: midazolam, diazepam, lorazepam, paraldehyde, valproate, phenobarbital, phenytoin, fosphenytoin, and levetiracetam. Dosage and administration route of intervention, as well as study characteristics are summarized in Table 1. Eight studies were conducted in untreated participants [8–11, 13–16], while eight studies were conducted in participants who required second-line therapy [12, 17–23].

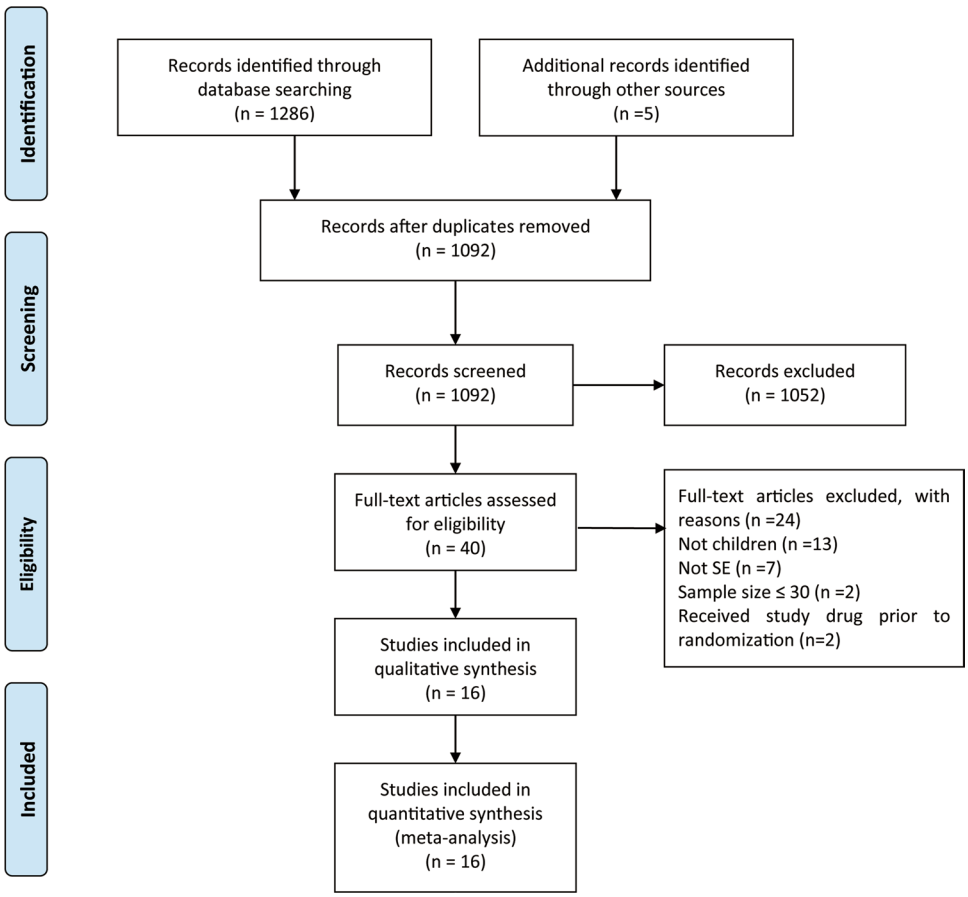

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. *SE* status epilepticus

Table 1 Study characteristics

Study, year	Country	Number of patients, sex ratio (M:F)	Age, mean ± SD (range)	Definition of SE	Drugs (dose/route)	Etiology of SE
Lahat, 2000 [8]	Israel	21 (13:8)	16 (6–38) mo	Lasting for at least 10 min	Midazolam (0.2 mg/kg IN)	Upper respiratory tract infection 48%
						Acute otitis media 29%
						Bronchopneumonia 14%
						Shigellosis 14%
						Other 19%
		23 (12:11)	18 (6–40) mo		Diazepam (0.3 mg/kg IV)	Upper respiratory tract infection 43%
						Acute otitis media 17%
						Bronchopneumonia 17%
						Shigellosis 22%
						Other 13%
Ahamed, 2006 [9]	Malawi	80 (44:36)	18.5 (9–33) mo	Generalized convulsions for over 5 min	Lorazepam (100 μg/kg IN)	Cerebral malaria 49%
						Protracted febrile convulsion 20%
						Acute bacterial meningitis 15%
						Metabolic derangement 15%
						Other 12.5%
		80 (43:37)	19.0 (10.5–36) mo		Paraldehyde (0.2 mL/kg IM)	Cerebral malaria 55%
						Protracted febrile convulsion 19%
						Acute bacterial meningitis 11%
						Metabolic derangement 15%
						Other 12.5%

Table 1 (continued)

Study, year	Country	Number of patients, sex ratio (M:F)	Age, mean ± SD (range)	Definition of SE	Drugs (dose/route)	Etiology of SE
Mpimbaza, 2008 [10]	Uganda	165 (82:83)	18.0 (11.5–36.0)	Convulsion or seizures for more than 5 min	Diazepam (0.5 mg/kg intrarectally)	Severe malaria 48% Cerebral malaria 15% Meningitis 6%; pneumonia 6% Epilepsy 4% Other 22%
		165 (84:81)	17.0 (10.5–30.0)		Midazolam (0.5 mg/kg intrabuccally)	Severe malaria 55% Cerebral malaria 14% Meningitis 5%; pneumonia 4% Epilepsy 4% Other 18%
Sreenath, 2010 [11]	India	90 (55:35)	84 ± 36.8 mo	Defined as continuous convulsive activity lasting for 5 min or more	Lorazepam (0.1 mg/kg IV)	Unprovoked seizure 66.6% Simple febrile seizure 16.6% Atypical febrile seizure 3.3% Pyogenic meningitis 4.4% Tuberculous meningitis 2.2% Viral meningoencephalitis 4.4% Other 2.2%
		88 (47:41)	78.7 ± 32.5		Diazepam (0.2 mg/kg IV) followed by phenytoin 18 mg/kg IV	Unprovoked seizure 72.7% Simple febrile seizure 7.9% Atypical febrile seizure 7.9% Pyogenic meningitis 3.4% Tuberculous meningitis 1.1% Viral meningoencephalitis 3.4% Other 3.3%

Table 1 (continued)

Study, year	Country	Number of patients, sex ratio (M:F)	Age, mean ± SD (range)	Definition of SE	Drugs (dose/route)	Etiology of SE
Malamiri, 2012 [12]	Iran	30 (16:14)	5 (3–16) y	Defined as a continuous, generalized, convulsive seizure lasting longer than 5 min	Valproate (20 mg/kg IV)	Remote symptomatic epilepsy 70% Idiopathic epilepsy 13% Prolonged febrile seizure 17%
		30 (21:9)	4 (3–11) y		Phenobarbital (20 mg/kg IV)	Remote symptomatic epilepsy 33% Idiopathic epilepsy 23% Prolonged febrile seizure 43%
Malu, 2013 [14]	Congo and Rwanda	202 (91:111)	35.5 (17.8–54) mo	Seizures lasted for more than 30 min or repeated ≥ 2 times without any recovery	Diazepam (0.1 mg/kg sublingually)	Cerebral malaria 58.9% Epilepsy 13.9% Meningitis 8.4% Other 18.8%
		234 (130:104)	35.5 (19–60) mo		Lorazepam (0.5 mg/kg intrarectally)	Cerebral malaria 65.8% Epilepsy 9.4% Meningitis 7.3% Other 17.5%
Chamberlain, 2014 [13]	USA	162 (87:75)	4.9 ± 4.9 y	Either current convulsion and (1) ≥ 3 convulsions within the preceding hour; (2) ≥ 2 convulsions with no recovery; or (3) current single convulsion of at least 5 min duration	Diazepam (0.2 mg/kg IV)	Febrile 35% Low levels of AEDs 8.6% Acute symptomatic 16.4% Remote symptomatic 9.3% Idiopathic 26.4% Other 4.4%
		148 (68:80)	4.8 ± 4.6 y		Lorazepam (0.1 mg/kg IV)	Febrile 30.1% Low levels of AEDs 9.8% Acute symptomatic 11.3% Remote symptomatic 10.5% Idiopathic 33.1% Other 4.5%

Table 1 (continued)

Study, year	Country	Number of patients, sex ratio (M:F)	Age, mean ± SD (range)	Definition of SE	Drugs (dose/route)	Etiology of SE
Momen, 2015 [15]	Iran	50 (31:19)	2 ± 1.1 y	Continuous, generalized, convulsive seizure lasting longer than 5 min	Midazolam (0.3 mg/kg IM)	Febrile 46% Remote symptomatic 30% Idiopathic 24%
		50 (27:23)	2.5 ± 1.4 y		Diazepam (0.5 mg/kg intrarectally)	Febrile 52% Remote symptomatic 20% Idiopathic 28%
Welch, 2015 [16]	USA	60 (35:25)	6.4 ± 4.8 y	Seizure activity persisting for more than 5 min or lack of return to baseline function between seizures within a 5-min interval	Midazolam (10 mg IM)	Idiopathic 40% Febrile 25% AED withdrawal 15% Other 19%
		60 (36:24)	6.9 ± 4.6 y		Lorazepam (4 mg IV)	Idiopathic 49% Febrile 19% AED withdrawal 8% Other 25%
Burman, 2019 [17]	South Africa	52 (26:26)	25.7 (13.1–65.6) mo	Defined as any convulsive seizure longer than 5 min	Phenobarbital (20 mg/kg IV)	Genetic 26.9% Infectious 3.8% Structural 46.2% Unknown 23.1%
		59 (32:27)	22.2 (14.8–46.3) mo		Phenytoin (20 mg/kg IV)	Genetic 23.8% Structural 61.9% Unknown 14.3%

Table 1 (continued)

Study, year	Country	Number of patients, sex ratio (M:F)	Age, mean ± SD (range)	Definition of SE	Drugs (dose/route)	Etiology of SE
Dalziel, 2019 [18]	Australia and New Zealand	114 (53:61)	4.0 ± 3.9 y	Defined as being convulsions for longer than 5 min; or ≥ 2 recurrent convulsions without recovery of consciousness between convulsions Persistent seizure failed first-line treatment	Phenytoin (20 mg/kg IV or intraosseously)	Febrile 72% Focal onset 12% Other 16%
		119 (59:60)	3.8 ± 3.8 y		Levetiracetam (40 mg/kg IV or intraosseously)	Febrile 73% Focal onset 12% Other 15%
Lyttle, 2019 [19]	UK	152 (75:77)	2.7 (1.3–5.9) y		Levetiracetam (40 mg/kg IV)	Febrile 41% Pre-existing epilepsy 30% First afebrile seizure 11% CNS infection 4% Indeterminate 7% Intracranial vascular event 1% Substance misuse 1% Other 18%
		134 (72:62)	2.7 (1.6–5.6) y		Phenytoin (20 mg/kg IV)	Febrile 43% Pre-existing epilepsy 34% First afebrile seizure 9% CNS infection 5% Intracranial vascular event 1% Indeterminate 5% Other 19%

Table 1 (continued)

Study, year	Country	Number of patients, sex ratio (M:F)	Age, mean ± SD (range)	Definition of SE	Drugs (dose/route)	Etiology of SE
Noureen, 2019 [20]	Pakistan	300 (216:84)	3.54 ± 0.24 y	Generalized convulsive SE that does not response to two doses of diazepam (0.2 mg/kg)	Levetiracetam (40 mg/kg IV)	Meningitis/encephalitis 43.3% Febrile 6% Epilepsy 17.3% Cerebral palsy and epilepsy 19.3% Neurodegenerative disorders and epilepsy 14%
		300 (190:110)	3.46 ± 0.22 y		Phenytoin (20 mg/kg IV)	Meningitis/encephalitis 40% Febrile 6.7% Epilepsy 16.6% Cerebral palsy and epilepsy 20.7% Neurodegenerative disorders and epilepsy 16%
Chamberlain, 2020 [21]	USA	225 (124:101)/85, 71, and 69 for levetiracetam, phenytoin, and valproate groups	6.1 ± 4.3 y	Convulsions longer than 5 min duration	Levetiracetam (60 mg/kg IV)	Unprovoked 47% Febrile illness 40% AED withdrawal or noncompliance4% CNS infection 2%
					Fosphenytoin (20 mg PE/kg IV)	Insufficient information to determine idiopathic 1%
					Valproate (40 mg/kg IV)	Other 5%
Nalisetty, 2020 [22]	India	29 (16:13)	32.9 ± 37.2 mo	Persistent convulsion to the pediatric emergency room after 5 min	Fosphenytoin (20 mg PE/kg IV)	Febrile 76% Encephalitis 7% Unprovoked 10% Fever provoked7%
		32 (16:16)	29.4 ± 31.2 mo		Levetiracetam (40 mg/kg IV)	Febrile 88% Encephalitis 6% Camphor poisoning 3% Fever provoked 3%

Table 1 (continued)

Study, year	Country	Number of patients, sex ratio (M:F)	Age, mean ± SD (range)	Definition of SE	Drugs (dose/route)	Etiology of SE
Vignesh, 2020 [23]	India	35 (19:16)	44 ± 43 mo	Continuous seizure for more than 5 min without recovery	Phenytoin (20 mg/kg IV)	Acute 46%
						Remote 25%
						Acute on remote 3%
						Febrile 6%
						Unknown 20%
		35 (21:14)	59 ± 44 mo		Valproate (20 mg/kg IV)	Acute 20%
						Remote 20%
						Acute on remote 6%
						Febrile 6%
						Unknown 48%
		32 (18:14)	58 ± 50 mo		Levetiracetam (20 mg/kg IV)	Acute 44%
						Remote 16%
						Febrile 6%
						Unknown 34%

AEDs anti-epileptic drugs, *CNS* central nervous system, *F* female, *IM* intramuscularly, *IN* intranasally, *IV* intravenously, *M* male, *min* minutes, *mo* months, *PE* phenytoin equivalents, *SD* standard deviation, *SE* status epilepticus, *y* years

3.2 Risk of Bias

Selection bias was the most frequent bias observed in 13 studies (seven studies judged to be high risk), followed by bias due to deviations from intended interventions in seven studies, randomization bias in five studies, and measurement bias in six studies (Fig. S1 of the ESM). Despite interventions not being blinded to participants and caregivers in some studies, outcome measurement was unlikely to be affected. Missing outcome and report selection biases were low.

3.3 Efficacy in First-Line Antiseizure Medications

Figure 2 shows the network of first- and second-line ASM comparisons. In total, 1686 patients were randomized to receive four ASMs as the first-line intervention, including midazolam, diazepam, lorazepam, and paraldehyde. The most frequently studied drug was diazepam. Direct and mixed comparison for seizure cessation between these drugs did not show significant differences (Figs. 3a, 5a). The point estimates of seizure cessation indicated that midazolam had superiority, followed by diazepam, lorazepam, and paraldehyde ($prob_{midazolam} = 49.44\%$ vs $prob_{diazepam} = 31.34\%$ vs $prob_{lorazepam} = 13.96\%$ vs $prob_{paraldehyde} = 5.27\%$, Fig. 4a).

Differences for recurrence within 24 h among first-line ASMs did not show statistical significance (Figs. 3c, 5b). Midazolam was superior to lorazepam, paraldehyde, and diazepam with respect to seizure recurrence within 24 h ($prob_{midazolam} = 58.26\%$ vs $prob_{diazepam} = 8.42\%$ vs $prob_{lorazepam} = 17.43\%$ vs $prob_{paraldehyde} = 15.89\%$, Fig. 4b). Therefore, midazolam had the greatest probability of controlling seizure and preventing recurrence within 24 h. There was no inconsistency between direct and indirect comparisons ($p > 0.05$). No evidence of heterogeneity was found ($I^2 < 25\%$, $p > 0.05$).

3.4 Efficacy in Second-Line Antiseizure Medications

In total, 1711 patients were randomized to receive five ASMs as the second-line intervention, including valproate, phenobarbital, phenytoin, fosphenytoin, and levetiracetam. These ASMs showed similar effects in seizure cessation (Figs. 3b, 5c). Phenobarbital and levetiracetam had superiority with respect to seizure cessation ($prob_{valproate} = 17.39\%$ vs $prob_{phenobarbital} = 39.10\%$ vs $prob_{phenytoin} = 6.04\%$ vs $prob_{fosphenytoin} = 5.61\%$ vs $prob_{levetiracetam} = 31.87\%$, Fig. 4c), whereas valproate was likely to have the best effect in preventing seizure recurrence ($prob_{valproate} = 68.49\%$ vs $prob_{phenobarbital} = 2.18\%$ vs $prob_{phenytoin} = 0.93\%$ vs $prob_{fosphenytoin} = 10.09\%$ vs $prob_{levetiracetam} = 18.32\%$, Figs. 4d, 5d). There was no inconsistency between direct and indirect comparisons ($p > 0.05$). No evidence of heterogeneity was found ($I^2 < 25\%$, $p > 0.05$).

3.5 Safety

The most common ASM-relevant adverse event was respiratory depression. Other adverse events such as arrhythmia, hypotension, and death were not eligible for quantitative analysis because of missing outcomes and null values. Hence, only respiratory depression was compared between studies. Seven first-line ASM studies [8–11, 13, 15, 16] and five second-line ASM studies [12, 17, 20, 21, 23] were eligible for quantitative synthesis. Compared with midazolam, diazepam and lorazepam had a slightly increased risk for respiratory depression ($RD_{diazepam\text{-}midazolam} = 0.07$, 95% CI -0.12 to 0.32; $RD_{lorazepam\text{-}midazolam} = 0.06$, 95% CI −0.14 to 0.29). Administration of midazolam had a lower probability of respiratory depression compared with diazepam and lorazepam (Figs. S2A and C of the ESM).

Among all these second-line ASMs, the risk of respiratory depression was slightly lower in levetiracetam compared with valproate ($RD_{levetiracetam\text{-}valproate} = -0.01$, 95%

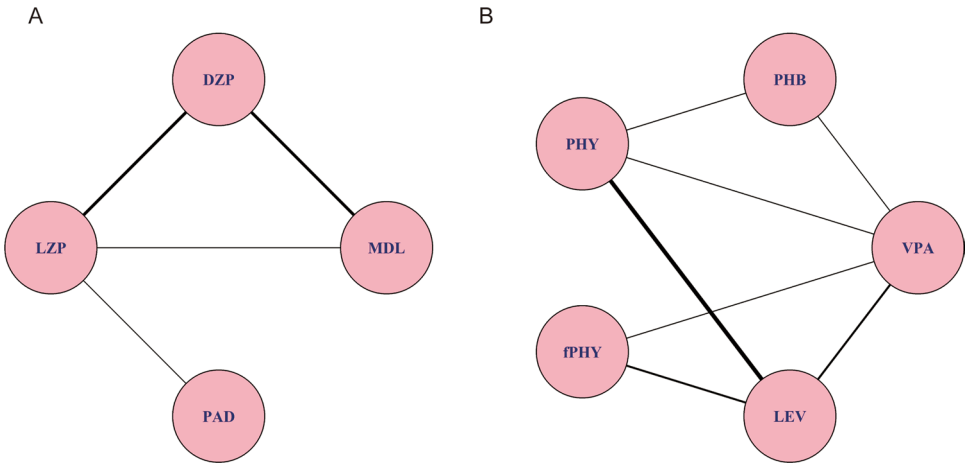

Fig. 2 Network of included studies. **a** First-line antiseizure medications and **b** second-line antiseizure medications. *DZP* diazepam, *fPHY* fosphenytoin, *LEV* levetiracetam, *LZP* lorazepam, *MDL* midazolam, *PAD* paraldehyde, *PHB* phenobarbital, *PHY* phenytoin, *VPA* valproate

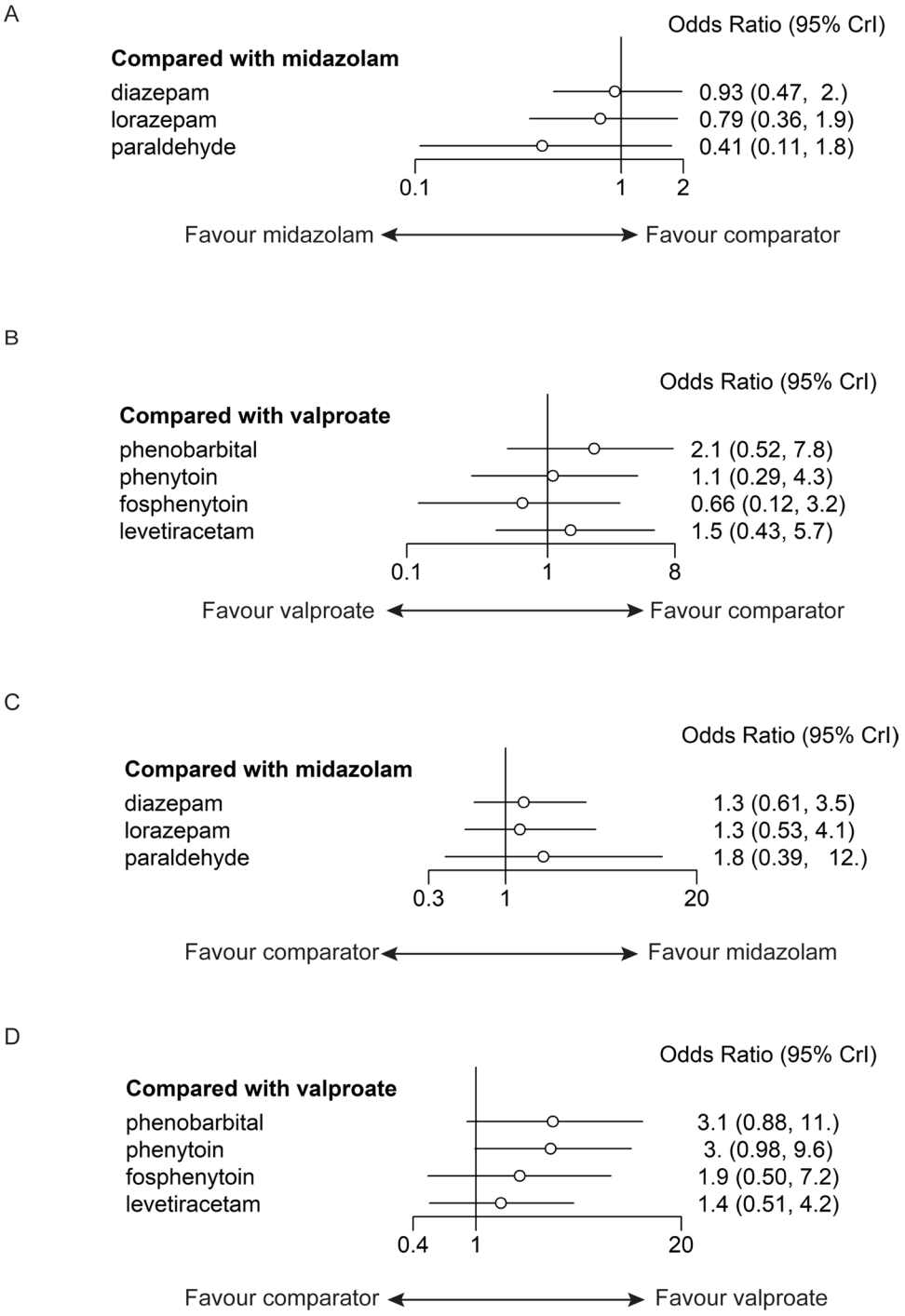

Fig. 3 Outcome comparison of antiseizure medications (ASMs). **a** seizure cessation for first-line ASMs; **b** seizure cessation for second-line ASMs; **c** seizure recurrence within 24 h for first-line ASMs; and **d** seizure recurrence within 24 h for second-line ASMs. *Crl* credible interval

CI −0.30 to 0.48, Fig. S2B and D of the ESM). Phenobarbital, phenytoin, and fosphenytoin showed an increased risk compared with valproate ($RD_{phenobarbital\text{-}valproate} = 0.06$, 95% CI −0.17 to 0.53; $RD_{phenytoin\text{-}valproate} = 0.11$, 95% CI −0.25 to 0.53; $RD_{fosphenytoin\text{-}valproate} = 0.18$, 95% CI −0.11 to 0.89). Analysis on admission to the ICU was performed exclusively in second-line ASM studies because most first-line ASM studies did not have sufficient information for pooled data. Phenobarbital significantly lowered the risk of admission to the ICU compared with fosphenytoin ($RD_{fosphenytoin\text{-}phenobarbital} = 0.56$, 95% CI 0.05–0.89). Despite phenobarbital not having significant differences compared to other second-line ASMs, it was more likely to reduce the probability of admission to the ICU (Fig. S2e, f of the ESM).

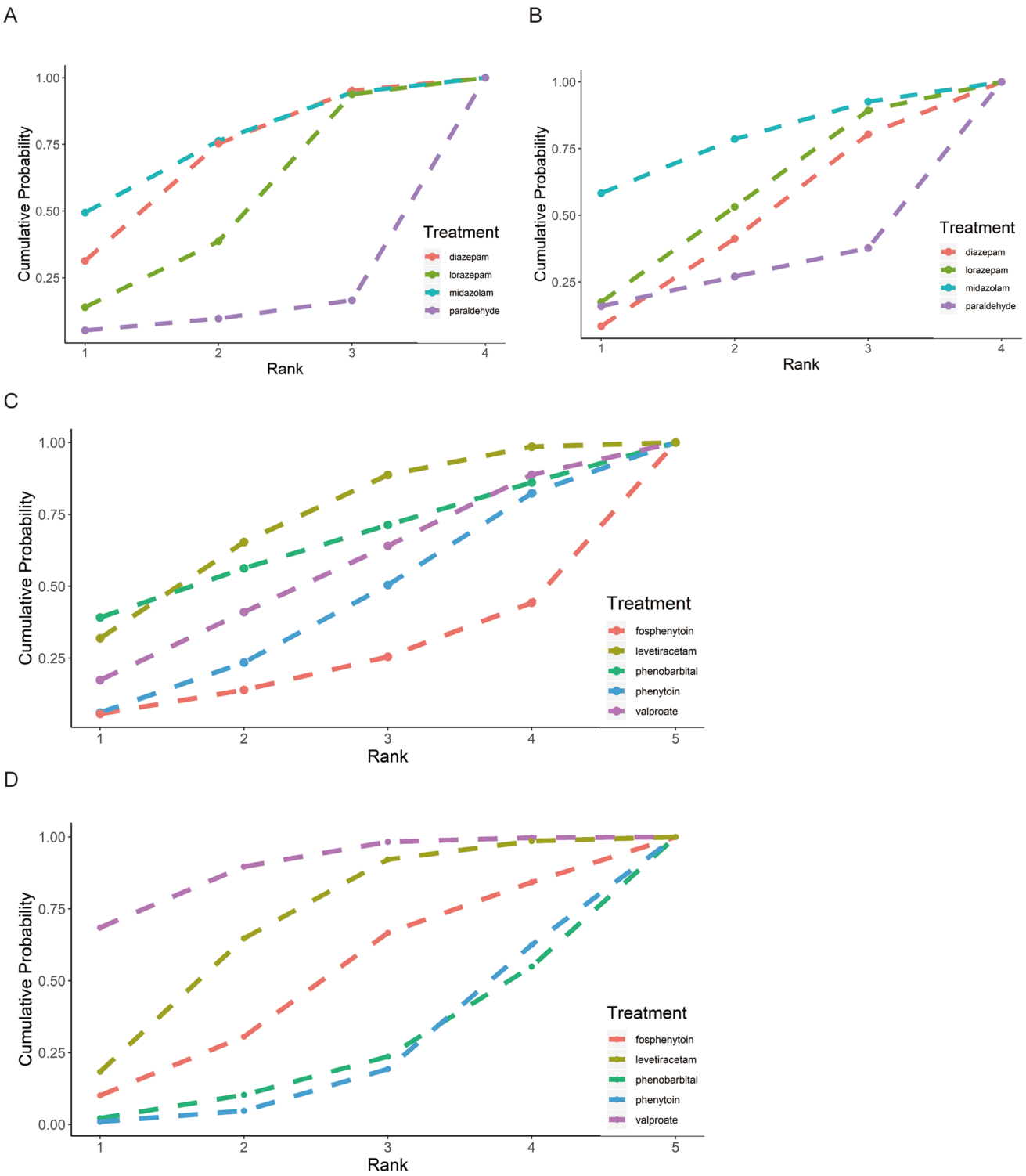

Fig. 4 Surface under the cumulative ranking curve. **a** seizure cessation in first-line antiseizure medications (ASMs); **b** seizure recurrence in first-line ASMs; **c** seizure cessation in second-line ASMs; and **d** seizure recurrence in second-line ASMs

4 Discussion

The present study provided evidence from a systematic analysis of RCTs conducted in pediatric patients with CSE. Four first-line ASMs and five second-line ASMs were assessed for their efficacy and safety in the pediatric population. The absence of significant differences between these ASMs may reflect the flaws of the small sample size and heterogeneity in

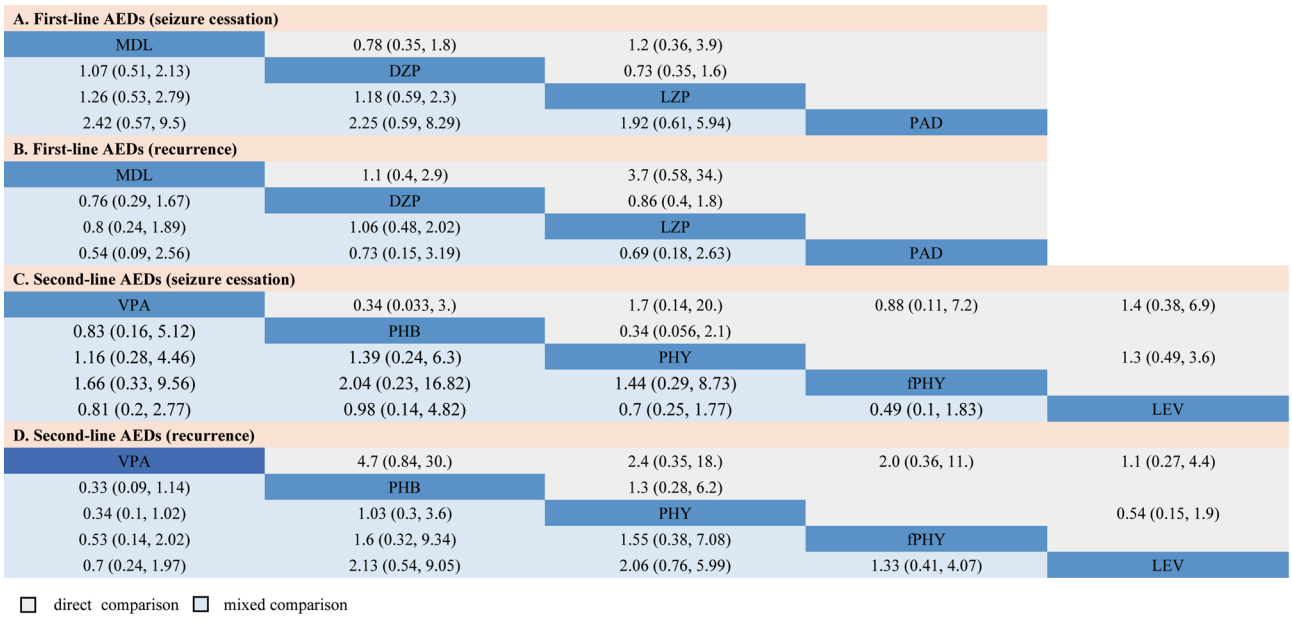

Fig. 5 Outcome comparison of antiseizure medications. Data were presented as odd ratios with 95% credible intervals for mixed comparisons or 95% confidence intervals for direct comparisons. *AEDs* antiepileptic drugs, *DZP* diazepam, *fPHY* fosphenytoin, *LZP* lorazepam, *LEV* levetiracetam, *MDL* midazolam, *PAD* paraldehyde, *PHB* phenobarbital, *PHY* phenytoin, *VPA* valproate

current RCTs. Otherwise, the differences were only of small magnitude yet to be demonstrated in a larger population.

This study provided a profile of the hierarchy of comparative effect in different ASMs. The best ranked first-line ASMs was midazolam, which had superiority to both primary and secondary outcomes (seizure cessation, recurrence, and respiratory depression). Diazepam was usually more frequently used in the emergency room. It required continuous intravenous infusion, which may cause acute respiratory depression, sedation, and hypotension. Our finding suggested that midazolam was probably a better option as a first-line treatment.

Phenobarbital ranked best among second-line ASMs for seizure cessation and admission to the ICU. Similar to the conclusion drawn by the present study, one high-quality study comparing phenobarbital with phenytoin found a significant difference in seizure cessation ($p = 0.003$) [17]. Phenobarbital as a traditional anticonvulsant may be more acceptable in resource-limited regions considering that it ranked best in the likelihood of achieving seizure cessation and reducing admission to the ICU. These advantages may help ease the financial burden and terminate seizure efficaciously. However, the side effects in cognition and behavior should also be taken into consideration.

Valproate had superiority with respect to preventing recurrence within 24 h and had an equally lower risk in respiratory depression compared with levetiracetam. The vast majority of valproate was metabolized by the cytochrome P450 enzyme in the liver [24]. A considerable adverse event of valproate was hepatotoxicity. However, few included studies reported gastrointestinal and hepatic adverse events.

Levetiracetam was a novel ASM safely used in children aged older than 4 years. The maximum dose of 60 mg/kg per day was acceptable [25]. According to a recent pairwise meta-analysis [26], the efficacy of levetiracetam was not significantly superior to phenytoin, which was consistent with this study. Despite no differences observed between levetiracetam and other second-line ASMs, it ranked the second-best option for cessation and preventing recurrence. Among six RCTs evaluating levetiracetam, only one low-quality study demonstrated levetiracetam was superior to phenytoin [20]. Two high-quality studies found that levetiracetam was not superior to phenytoin or other ASMs, e.g., fosphenytoin and valproate [18, 21]. Its unique metabolic kinetics independent of the cytochrome P450 enzyme exerted less effect on drug–drug interactions. Few adverse events were reported, e.g., sedative and behavioral effects [27]. Consistently, we found that levetiracetam had the lowest probability of developing respiratory depression. However, this drug was not available in many regions worldwide. Therefore, selection of the optimal second-line ASMs should be balanced between accessibility, tolerability, etiology, and patient characteristics.

Brivaracetam is structurally similar to levetiracetam. Despite these two drugs targeting the same molecule, SV2A, brivaracetam showed a more than 15-fold higher binding

affinity and faster response [28]. Several randomized clinical studies evaluated the efficacy and safety of brivaracetam in adult focal seizures. A meta-analysis demonstrated that brivaracetam was not inferior to eslicarbazepine acetate, lacosamide, and perampanel [29]. To date, few clinical studies have evaluated brivaracetam in the treatment of SE. According to the latest systematic review, brivaracetam could be safely used but still lacks evidence to evaluate its efficacy in the treatment of SE [30].

Studies have highlighted the neuronal machinery of SE, involving loss of GABA-mediated inhibition and sustained glutamate-mediated excitation [4]. The AMPA receptor induced seizures by synchronizing glutamatergic excitatory signals, thus it may be a potential therapeutic target. Perampanel is an orally active, selective, non-competitive AMPA receptor agonist that inhibits AMPA-mediated Ca^{2+} influx and neuronal excitation [31]. Because of its pharmacodynamics, perampanel could be a promising treatment for seizures. It becomes a welcome adjunctive treatment for focal seizures and primary generalized tonic–clonic seizures, but few studies investigated its role in the treatment of SE [32, 33]. A systematic review summarized current evidence supporting the administration of perampanel in SE. Perampanel is well tolerated in patients with SE. However, the efficacy of perampanel in SE treatment remains elusive [32]. Therefore, these studies revealed the urgent need for more well-designed high-quality studies investigating the efficacy of novel drugs, e.g., perampanel and brivaracetam in the treatment of SE.

Paraldehyde was commonly used as first- and second-line ASMs in sub-Saharan Africa. Focal irritation, inconvenience for infusion, and high cost were major disadvantages. Moreover, patients treated with paraldehyde had a higher probability of receiving additional dose of ASMs (lorazepam, 10% vs paraldehyde, 26%, $p = 0.007$) [9]. In the present study, paraldehyde ranked worst for efficacy among other first-line ASMs. However, only one study investigating paraldehyde was eligible for analysis [9]. The evidence was insufficient to validate its efficacy and safety.

In second-line ASMs, phenytoin and fosphenytoin ranked worst for seizure cessation. This may reflect the flaws of restricted infusion speed and prolonged infusion duration to avoid respiratory and cardiac adverse events. Phenytoin and fosphenytoin did not show significant differences in seizure cessation or recurrence (Fig. 3b, d). The risk of respiratory depression was similar (Fig. S2b of the ESM).

Some clinical studies have evaluated ASMs in adult patients with SE. A recent network meta-analysis revealed that high-dose phenobarbital ranked best for SE control and preventing seizure recurrence, while phenytoin ranked worst for seizure cessation. Lacosamide and valproate represented a safer option. Phenobarbital ranked worst in safety outcomes because of the very high dosage used in patients with SE [34]. In adult patients with SE, the beneficial effect obtained in the phenobarbital arm was most likely due to the very high dosage. However, the dosage used in pediatric patients was regularly recommended (20 mg/kg), suggesting that the dosage did not largely affect the superiority of phenobarbital over other ASMs in pediatric patients with SE. Moreover, an updated network meta-analysis including the Established Status Epilepticus Treatment Trial (ESETT) was presented to compare those ASMs with appropriate dosages in clinical practice [35]. No significant difference was identified for seizure cessation, seizure freedom at 24 h, respiratory depression, and hypotension. Valproate ranked the best with respect to the efficacy outcome and had the lowest probability in respiratory depression. In the present study, similar results were observed. Valproate and levetiracetam were comparable in efficacy and ranked as the best two medications for safety outcomes, whereas phenytoin and fosphenytoin ranked as the worst medications for seizure cessation and safety outcome.

The sample size in half of the included studies was small, which may increase the risk for statistical type II error and cause a false-negative result in RCTs [36]. Clinical heterogeneity in age, etiology, and admission interval may also cause potential biases. The most common cause of SE was febrile SE, which limited to children aged less than 5 years, whereas cryptogenic and remote symptomatic SE were common in older children [1]. Acute symptomatic SE including metabolic disorders, cerebrovascular disease, central nervous system infection, anoxia, electrolyte abnormality, and traumatic brain injury was strongly associated with a poorer prognosis [37]. A selected population may produce a distinct outcome, interfering with the validity of pooled data. Moreover, SE may have persisted for a different time interval before receiving any intervention. A longer duration of SE predicted a worse outcome. Therefore, clinical heterogeneity could be another reason for the absence of clear-cut differences between ASMs. Most included studies were not designed to investigate clinical outcomes of ASMs in stratified subgroups. Consequently, it was impossible to identify interfering covariates by a subgroup analysis or a meta-regression in the present study. Because of these limitations, the interpretation of this study should be cautious.

The present study was the first to compare the efficacy and safety of different ASMs for CSE in pediatric patients. We provided a hierarchy of different ASMs for first- and second-line interventions in pediatric patients with CSE. Although a network meta-analysis could not be a substitute for head-to-head clinical trials, it may provide solid evidence and supplementary guidance for clinical decision making.

5 Conclusions

This study demonstrated the hierarchy of comparative effect on the efficacy and safety of different ASMs in pediatric patients with CSE. Midazolam ranked as the best first-line treatment. Levetiracetam and valproate are better tolerated options with no inferiority compared to other second-line treatments. Phenobarbital had superiority in seizure cessation and ICU admission, thus could be a better option in resource-limited regions. To date, few high-quality studies have demonstrated the superiority of one ASM over the other. This study highlighted current limitations and the need for high-quality studies. It may provide useful information for clinical practice under different circumstances.

Declarations

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest Yihao Zhang, Yingjie Liu, Qiao Liao, and Zhixiong Liu have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability The data used in this study were fully available in databases.

Code availability Not applicable.

Author contributions YZ and YL equally contributed to this manuscript in conception, data extraction, quality assessment, data analysis, and drafting. QL and ZL revised the manuscript.

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