National Institute for Health and Care Excellence

Draft for Consultation

Epilepsies in children, young people and adults: diagnosis and management

[09] Evidence review: Antiseizure medication: Status epilepticus

NICE guideline

Evidence reviews underpinning recommendations 7.1.1 – 7.1.12 the NICE guideline

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Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1 Anti-seizure medication: Status epilepticus

1.1 Introduction

Status epilepticus is a serious medical emergency characterised either by continued seizures or by a lack of full recovery between seizures. People with status epilepticus require urgent intervention to limit their risk of neurological harm and death, particularly from generalised tonic-clonic status epilepticus. Adherence to standard management protocols, including early intervention, is important to improve outcomes of status epilepticus in adults and children. Such protocols need to be built upon the best evidence to guide the most effective and timely interventions in both community and hospital settings. This review evaluates how to optimise care for people with status epilepticus up to the point of considering anaesthesia.

1.2 Review question Monotherapy

What anti-seizure medications (monotherapy) are effective in the treatment of status epilepticus?

1.2.1 Summary of the protocol

For full details, see the review protocol in Appendix A: section A.1.

Table 1: PICO characteristics of review question

Population	Inclusion: Children, young people and adults with status epilepticus (convulsive and non-convulsive) Strata: Convulsive status epilepticus Non-convulsive status epilepticus (focal, myoclonic, absence) Exclusion: New-born babies (under 28 days) with acute symptomatic seizures
Interventions	Brivaracetam Carbamazepine (for focal motor status) Chlormethiazole (clomethiazole) Clobazam Clonazepam (for myoclonic status) Chloral hydrate Diazepam Eslicarbazepine Fosphenytoin Gabapentin General anaesthetic induction agents Immunotherapy Intravenous immunoglobulin Lacosamide Levetiracetam Lorazepam Midazolam Oxcarbazepine Paraldehyde Perampanel Phenobarbital (phenobarbitone) Phenytoin

	Pregabalin Rufinamide Steroids (methylprednisolone, prednisolone) Stiripentol Topiramate Valproate (sodium valproate/valproic acid) Zonisamide Dose according to prescriber discretion and/or local protocols
Comparisons	• One drug vs placebo/no treatment • One drug vs another drug
Outcomes	• mortality (including SUDEP) • time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, up 24 hours for convulsive, non-convulsive- up to 1 month • time to event seizure cessation • seizure recurrence < within less than 24 hours after administration of monotherapy • time to seizure recurrence after administration of monotherapy • quality of life (QOLIE-31, QOLIE-AD-48) • length of ICU stay • length of hospital stay • mean Glasgow outcome scale (% difference in the means between the two groups) • adverse events ○ respiratory depression ○ hypotension ○ frequency of endotracheal intubation ○ ICU admission ○ neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance • healthcare resource use
Study design	• RCTs • Systematic reviews of RCTs Exclusion: Non-English publications, non-randomised studies, conference abstracts It is anticipated that there will be sufficient RCT evidence that there is no need to search for non-randomised studies.

1.2.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.2.3 Effectiveness evidence

1.2.3.1 Included studies

Twenty two studies assessing monotherapy in status epilepticus (SE) were included in the review[5, 7, 10, 13, 38, 41, 57, 59, 87, 110, 112, 115, 125, 126, 128, 130, 187, 189, 215, 217, 221, 239]these are summarised in Table 2 below. Fifteen studies were in children, 3 in adults and 2 in adults and children. Three reports for one study have also been included. Evidence was found for the following interventions: diazepam, levetiracetam, lorazepam, midazolam, paraldehyde and valproate. The majority of the studies were conducted in the emergency department (ED). All studies assessed those with convulsive seizures. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in Appendix C: section C.1, study evidence tables in Appendix D: section D.1, forest plots in Appendix E: section E.1, and GRADE tables in Appendix F: section F.1.

1.2.3.2 Excluded studies

See the excluded studies list in Appendix I:.

1.2.4 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention	Comparison	Population Age Top 3 causes of SE	Outcomes	Comments
Ahmad 2006[5] Malawi	Intranasal Lorazepam: 100 micrograms/kg n=80	Intramuscular Paraldehyde: 0.2ml/kg n=80	Children [median (IQR)] Lorazepam – 18.5 months (9 to 33) Paraldehyde – 19 months (10.5 to 36) Lorazepam Cerebral malaria: 49% Protracted febrile convulsion: 20% Metabolic derangement: 15% Paraldehyde Cerebral malaria: 55% Protracted febrile convulsion: 19% Metabolic derangement: 15%	Mortality at hospital discharge (no further details given) Seizure recurrence within 24 hours Termination of SE within 10 min Time to seizure cessation	ED
Alldredge 2001[7] USA	Intravenous diazepam: 5 mg n=68	Placebo n=71 Intravenous lorazepam: 2 mg n=66	Adults Diazepam Low blood level of AEDs: 25.0% Refractory epilepsy:11.8% Alcohol abuse: 11.8% Placebo Low blood level of AEDs: 23.9% Refractory epilepsy:8.5% Alcohol abuse: 9.9%	Mortality at hospital discharge (no further details given) Cessation of SE before arrival to ED	Treatment out-of-hospital before arrival at ED Mean time (SD) interval from study treatment to arrival at ED: Diazepam: 15.9 (9.3) min Placebo: 16.5 (8.2) min

Study	Intervention	Comparison	Population Age Top 3 causes of SE	Outcomes	Comments
			Lorazepam Low blood level of AEDs: 16.7% Refractory epilepsy:13.6% Alcohol abuse: 9.1%		Lorazepam: 16.2 (9.2) min
Appleton 1995 UK[10]	Intravenous/rectal lorazepam: 0.05 to 1.0 mg/kg, intravenously over 15 to 30 sec, children convulsing after 7 to 8 min after initial dose received a second dose n=53	Intravenous/rectal diazepam 0.3 to 0.4 mg/kg over 15 to 30 sec, children convulsing after 7 to 8 min after initial dose received a second dose n=33	Children (mean) Lorazepam (IV = 6.6 years, rectal = 3.3 years) Known epilepsy: 64% Neurological disorder: 24% Diazepam (IV = 5.2 years, rectal = 3.8 years) Known epilepsy: 64% Neurological disorder 22%	Cessation of seizures after 7-8 min Seizure recurrence within 24 h Hypotension Time to seizure cessation	ED
Ashrafi 2010[13] Iran	Buccal midazolam: 0.3 to 0.5 mg/kg n=49	Rectal diazepam: 0.5 mg/kg n=49	Children (median) Buccal midazolam (24 months) Generalised tonic-clonic seizures: 86% Myoclonic seizures: 14% Diazepam (48 months) Generalised tonic-clonic seizures: 86% Myoclonic seizures: 10% Focal tonic seizure: 2%	Cessation of SE within 5 min	ED
Chamberlain 1997[38]	Intravenous Midazolam: 0.2mg/kg (maximum 7 mg)	Intravenous Diazepam: 0.3mg/kg (maximum 10 mg)	Children (range 3 to 112 months) Midazolam	Time to cessation after drug administration Seizure recurrence within 24 hours	ED

Study	Intervention	Comparison	Population Age Top 3 causes of SE	Outcomes	Comments
USA	n=13	n=11	Generalised tonic clonic: 77% Partial motor seizures: 23% Diazepam Generalised tonic clonic: 45% Partial motor seizures: 55%	Respiratory depression	
Chamberlain 2014[41] USA	Intravenous Diazepam: dose of 0.2 mg/kg of diazepam (maximum dose, 8 mg) n=162	Intravenous Lorazepam: 0.1 mg/kg of lorazepam (maximum dose, 4 mg) n=148	Children (range 3 months to 17.8 years) Diazepam Febrile: 35% Low levels of anti-epileptic drugs: 8.6% Acute symptomatic: 16.4% Lorazepam Febrile: 30.1% Low levels of anti-epileptic drugs: 9.8% Acute symptomatic: 11.3%	Termination of seizure within 10 min Seizure recurrence within 24 hours Respiratory depression	ED
Fisgin 2002[57] Turkey	Rectal diazepam: 0.3 mg/kg n=22	Intranasal midazolam: 0.2 mg/kg in 30 sec n=23	Children (mean) Diazepam (2.02 years) Generalised tonic clonic 64% Simple febrile: 14% Focal secondary generalised: 14% Midazolam (3.8 years) Generalised tonic clonic 62% Simple febrile: 30% Focal secondary generalised: 4%	Seizure cessation at 10 min	ED

Study	Intervention	Comparison	Population Age Top 3 causes of SE	Outcomes	Comments
Gathwala 2012[59] India	Intravenous lorazepam: 0.1 mg/kg diluted in 3 to 5 cc normal saline, dose infused over 1 to 2 min at 1 to 2 mg/min, maximum dose was 4 mg per dose and if seizure persisted, one more dose was given after an interval of 5 to 10 min n=40	Intravenous diazepam: 0.3 mg/kg diluted in 3 to 5 cc normal, dose infused over 2 min at 2mg/min, maximum dose was 5 mg in children > 5 years old and 10 mg in children 5 years or older if seizure persisted a repeat dose was given after an interval of 5 to 10 min n=40 Intravenous midazolam: 0.1 mg/kg diluted in 3 to 5 cc normal saline, dose infused over 1 to 2 min at 1 to 2 mg/min, maximum dose was 5 mg per dose and if seizure persisted, one more dose was given after an interval of 5 to 10 min n=40	Children (mean [SD]) Lorazepam (5.28 [2.97]) Seizure disorder: 83% Meningitis/encephalitis: 15% Neurocysticercosis: 2% Diazepam (6.19 [3.63]) Seizure disorder: 88% Meningitis/encephalitis: 10% Neurocysticercosis: 2% Midazolam (4.82 [2.48]) Seizure disorder: 85% Meningitis/encephalitis: 13% Neurocysticercosis: 2%	Mean duration of seizure Respiratory depression	ED

Study	Intervention	Comparison	Population Age Top 3 causes of SE	Outcomes	Comments
Lahat 2000[87] Israel	Intranasal Midazolam: 0.2 mg/kg. Midazolam solution (5 mg/ml) was dripped by syringe into both nostrils in equal doses, and an intravenous line was immediately introduced n=21	Intravenous Diazepam: dose of 0.3 mg/kg, the maximum dose being 10 mg. n=23	Children (range 6 to 40 months) Midazolam Upper respiratory tract infection: 43% Acute otitis media: 26% Bronchopneumonia: 14% Diazepam Upper respiratory tract infection: 47% Acute otitis media: 17% Bronchopneumonia: 17%	Time to cessation of seizure after drug administration Treatment failure Seizure recurrence Adverse events	Paediatric ED
Mahmoudian 2004[110] Iran	Intranasal Midazolam: solution (5mg/ml) was dropped by syringe into both nostrils in equal doses to those with even numbers and an intravenous line was immediately introduced. n=35	Intravenous diazepam: 0.2mg/kg was administered to patients with odd numbers after an intravenous line was introduced n=35	Children (range 2 months to 15 years) Midazolam Hypocalcaemia: 0% Febrile convulsions: 40% CNS infection: 11% Diazepam Hypocalcaemia: 5% Febrile convulsions: 3% CNS infection: 29%	Seizure control within 10 min Mean interval between drug administration and seizure control Adverse events	Hospital
Malu 2014[112] Democratic Republic of the Congo, Rwanda	Rectal diazepam: was administered at a dose of 0.5 mg/kg of body weight of a 1mg/mL reconstituted solution n=202	Sublingual Lorazepam: was administered at a dose of 0.1 mg/kg of body weight, a 1 mg tablet was administered to	Children (Interquartile range 17.75 months to 60 months) Diazepam Cerebral malaria: 59%	Mortality at 24 hours Seizure cessation within - 5 min - 10 min - 20 min	Hospital

Study	Intervention	Comparison	Population Age Top 3 causes of SE	Outcomes	Comments
		children between 6 and 36 months old and 2.5 mg for those older than 4 years n=234	Epilepsy: 14% Meningitis: 8% Lorazepam Cerebral malaria: 66% Epilepsy: 9% Meningitis: 7%	Seizure recurrence within 24 hours	
Mcintyre 2005[115] UK	Buccal midazolam: the dose was determined by the child's age and was designed to give about 0.5 mg per kg (2.5 mg for children aged 6 to 12 months, 5 mg for 1 to 4 years, 7.5mg for 5-9 years, 10 mg for 10 years and older), the intravenous preparation of midazolam hydrochloride, filtered through a needle or straw, was administered into the buccal cavity between the gum and cheeks n=92	Rectal diazepam: the dose was determined by the child's age and was designed to give about 0.5 mg per kg (2.5 mg for children aged 6 to 12 months, 5 mg for 1 to 4 years, 7.5mg for 5-9 years, 10 mg for 10 years and older n=85	Children (Interquartile range 1 to 6 years) No information given on seizure causes	Seizure cessation within 10 min Seizure recurrence Respiratory depression Time (min) to stop seizing after treatment	ED
Misra 2006[126] India	Valproate: received sodium valproate 30 mg/kg in 100 ml saline infused over 15 min n=35	Phenytoin: received Phenytoin sodium 18mg/kg in 100 ml saline infused immediately at a rate of 50mg/min	Children and adults (range 1 to 85 years; 12 participants aged 15 or under, 56 participants aged over 15) Valproate	Termination of SE after drug administration Seizure recurrence within 24 hours	N/A

Study	Intervention	Comparison	Population Age Top 3 causes of SE	Outcomes	Comments
		n=33	CNS infection: 60% Cerebrovascular accident: 9% Metabolic: 29% Phenytoin CNS infection: 52% Cerebrovascular accident: 18% Metabolic: 18%	Seizure freedom at 24 hours Respiratory depression	
Misra 2012[125] India	Lorazepam: 0.1 mg/kg in 10 ml saline IV in 2–4 min n=41	Levetiracetam: 20 mg/kg infused in 15 min n=38	Adults (mean=Lorazepam: 38.9, Levetiracetam: 39.16) Lorazepam CNS infection:54% Stroke: 15% Drug withdrawal: 2% Levetiracetam CNS infection: 42% Stroke: 26% Neurocysticercosis: 3%	Mortality at hospital discharge (no further details given) Termination of SE within 30 min Seizure recurrence within 24 hours Seizure freedom at 24 hours Respiratory failure hypotension	Hospital
Momen 2015[128] Iran	Intramuscular midazolam: used with a dose of 0.3 mg/kg, injected into the left quadriceps muscle if the child was younger than 2 and if the child was older than 2 the left deltoid muscle was considered for injection.	Rectal Diazepam: a dose of 0.5mg/kg was given. n=50	Children (Mean, SD) Midazolam – 2 years (1.1) Febrile status: 46% Remote symptomatic: 30% Idiopathic: 24% Diazepam – 2.5 years (1.4) Febrile status: 52%	Drug treatment successful Seizure recurrence within 60 min Time from arrival to stopping seizures Respiratory depression	ED

Study	Intervention	Comparison	Population Age Top 3 causes of SE	Outcomes	Comments
	n=50		Remote symptomatic: 20% Idiopathic: 28%		
Mpimbaza 2008[130] Uganda	Rectal diazepam and placebo midazolam: packaged in 2ml plastic syringes, both drugs were administered at ~0.5mg/kg (2.5 mg for 3-11 months, 5mg for 1-4 years, 7.5 for 5-9 years and 10mg for 10-12 years n=165	Buccal midazolam and placebo diazepam: drugs were administered at ~0.5mg/kg (2.5 mg for 3-11 months, 5mg for 1-4 years, 7.5 for 5-9 years and 10mg for 10-12 years n=165	Children (interquartile range: 10.5 months to 36 months) Diazepam Febrile convulsion: 69.7% Generalised convulsion: 81.2% Focal: 18.8% Midazolam Febrile convulsion: 73.3% Generalised convulsion: 81.8% Focal: 18.2%	Mortality at hospital discharge (no further details given) Seizure cessation within 10 min Time to cessation of seizure Seizure recurrence within 1 hour of initial control Seizure recurrence within 24 hours Respiratory depression Time to cessation of seizure	Acute Care Unit (ACU), the paediatric emergency unit of Mulago Hospital and the national referral hospital in Kampala.
Silbergleit 2012[187, 189, 239] USA	Intramuscular midazolam and intravenous placebo: all adults and those children with an estimated body weight of more than 40 kg received 10 mg of intramuscular midazolam followed by intravenous placebo, in children with an estimated weight of 13 to 40 kg, the active	Intravenous lorazepam and intramuscular placebo: all adults and those children with an estimated body weight of more than 40 kg received intramuscular placebo followed by 4 mg of intravenous lorazepam, in children with an	Children and Adults (Mean, SD) Midazolam – 43 years (22) (range=0 to 102) Noncompliance with or discontinuation of anticonvulsant therapy: 31% Idiopathic or breakthrough status epilepticus: 27% Coexisting condition that lowered seizure threshold: 7%	Termination of SE at time of arrival at ED Seizure recurrence within 24 hours Length of hospital stay Length of ICU stay Hypotension	ED

Study	Intervention	Comparison	Population Age Top 3 causes of SE	Outcomes	Comments
	treatment was 5 mg of intramuscular midazolam n=448	estimated weight of 13 to 40 kg, the active treatment was 2 mg of intravenous lorazepam n=445	Lorazepam – 44 years (22) (range=1 to 94) Noncompliance with or discontinuation of anticonvulsant therapy: 32% Idiopathic or breakthrough status epilepticus: 27% Coexisting condition that lowered seizure threshold: 7%		
Thakker 2013[215] India	Intranasal midazolam: (0.2 mg/kg), midazolam solution (5 mg/ml) was dripped by syringe into both nostrils in equal doses, and an intravenous line was immediately introduced n=27	Intravenous diazepam: (0.3 mg/kg) n=23	Children (mean, SD) Midazolam – 3.84 years (2.93) Febrile convulsion: 11% Seizure disorder: 26% CNS infection: 26% Diazepam Febrile convulsion: 9% Seizure disorder: 26% CNS infection: 26%	Time to cessation after drug administration Treatment successful Seizure recurrence within 24hours Respiratory depression	Paediatric ED
Tonekaboni 2012[217] Iran	Buccal midazolam: 2.5 mg for children aged 6-12 months, 5 mg for 1-4 years, 7.5 mg for 5-9 years, and 10 mg for 10 years or older n=32	Intravenous diazepam: 0.3 mg/kg/dose and through an intravenous line n=60	Children (mean, SD = 17.5 months (10.1)) Midazolam Tonic seizures: 28% Tonic-clonic seizures: 56% Atonic seizures: 16% Diazepam Tonic seizures: 18% Tonic-clonic seizures: 67% Atonic seizures: 15%	Termination of seizure within 10 min Time to cessation after drug administration Hypotension	The paediatric emergency ward of Mofid Children's Hospital

Study	Intervention		Comparison	Population Age Top 3 causes of SE	Outcomes	Comments
Treiman 1998[221] USA	Lorazepam: administered by means of Tubex injection at a maximal rate of 0.5 ml per min. n=136	Phenobarbital: administered at a rate of 1 ml per min to produce the maximal rates of drug infusion n=124	Phenytoin: administered at a rate of 1 ml per minute to produce the maximal rates of drug infusion. n=127	Adults (mean= overt: 58.6 years, subtle: 62 years) Overt SE Remote neurologic cause: 69.5% Acute neurologic cause: 27.3% Life-threatening medical condition: 32% Cardiopulmonary arrest: 6.3% Toxic effects of therapeutic or recreational Drug: 6.3% Alcohol withdrawal: 6.5% Subtle SE Remote neurologic cause: 34.3% Acute neurologic cause: 37.3% Life-threatening medical condition: 56.7% Cardiopulmonary arrest: 38.1% Toxic effects of therapeutic or recreational Drug: 5.2% Alcohol withdrawal: 0.7%	Hypotension	Veterans Affairs medical centres and 6 affiliated university hospitals

See Appendix D: section D.1 for full evidence tables.

1.2.5 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Diazepam versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Diazepam (95% CI)
Termination of SE at time of arrival at ED: adults	139 (1 study)	MODERATE[1] due to risk of bias	RR 2.02 (1.19 to 3.42)	211 per 1000	215 more per 1000 (from 40 more to 511 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 4: Clinical evidence summary: Diazepam versus drugs (lorazepam, or midazolam)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Drug	Risk difference with Diazepam (95% CI)
Mortality - vs lorazepam: children	436 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.99 (0.8 to 4.95)	30 per 1000	30 more per 1000 (from 6 fewer to 118 more)
Mortality - vs midazolam: children	330 (1 study)	LOW[2] due to imprecision	RR 1.5 (0.63 to 3.57)	48 per 1000	24 more per 1000 (from 18 fewer to 125 more)
Termination of SE at time of arrival at ED - vs lorazepam: adults	134 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 0.72 (0.51 to 1.01)	591 per 1000	165 fewer per 1000 (from 290 fewer to 6 more)
Termination of SE within 5 min - vs midazolam: children	98 (1 study) 5 min	MODERATE[2] due to imprecision	RR 0.82 (0.71 to 0.94)	1000 per 1000	180 fewer per 1000 (from 60 fewer to 290 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Drug	Risk difference with Diazepam (95% CI)
Termination of SE within 5 min - vs lorazepam: children	436 (1 study) 5 min	LOW[1,2] due to risk of bias, imprecision	RR 1.37 (1.05 to 1.8)	278 per 1000	103 more per 1000 (from 14 more to 222 more)
Termination of seizure within 10 min - vs midazolam: children	714 (6 studies) 10 min	VERY LOW[1,2,3] due to risk of bias, imprecision, inconsistency	RR 0.87 (0.71 to 1.08)	744 per 1000	97 fewer per 1000 (from 216 fewer to 59 more)
Termination of seizure within 10 min - vs lorazepam (rectal/sublingual): children	436 (1 study) 10 min	MODERATE[1] due to risk of bias	RR 1.41 (1.24 to 1.62)	560 per 1000	230 more per 1000 (from 134 more to 347 more)
Termination of seizure within 10 min - vs lorazepam (IV administration): children	273 (1 study) 10 min	MODERATE[1] due to risk of bias	RR 0.99 (0.85 to 1.14)	729 per 1000	7 fewer per 1000 (from 109 fewer to 102 more)
Termination of seizure within 20 min - vs lorazepam: children	436 (1 study) 20 min	MODERATE[1] due to risk of bias	RR 1.1 (1.02 to 1.18)	829 per 1000	83 more per 1000 (from 17 more to 149 more)
Time to clinical seizure cessation - vs lorazepam: children	80 (1 study)	MODERATE[2] due to imprecision		The mean time to clinical seizure cessation in the control groups was 91.2	The mean time to clinical seizure cessation in the intervention groups was 6.26 lower (20.27 lower to 7.75 higher)
Time to cessation after drug administration - vs midazolam: children	360 (6 studies)	MODERATE[1] due to risk of bias		The mean time to cessation after drug administration in the control groups was 1.25	The mean time to cessation after drug administration in the intervention groups was 1.45 lower (1.62 to 1.29 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Drug	Risk difference with Diazepam (95% CI)
Seizure recurrence within 24 hours - vs midazolam (UK): children	535 (6 studies) 24 hours	LOW[1,2] due to risk of bias, imprecision	RR 1.34 (1.03 to 1.76)	216 per 1000	262 more per 1000 (from 73 more to 1.64 more)
Seizure recurrence within 24 hours - vs lorazepam: children	634 (2 studies) 24 hours	MODERATE[1] due to risk of bias	RR 1.06 (0.87 to 1.29)	372 per 1000	22 more per 1000 (from 48 fewer to 108 more)
Adverse events, respiratory depression - vs midazolam: children	875 (8 studies)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.67 (0.66 to 4.22)	14 per 1000	14 fewer per 1000 (from 5 fewer to 44 more)
Adverse events, respiratory depression - vs midazolam: children	390 (2 studies)	MODERATE[2] due to imprecision	Peto OR 1.49 (0.95 to 2.34)	287 per 1000	80 more per 1000 (from 10 fewer to 170 more)
Adverse events, hypotension: - vs midazolam: children	92 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.69 (0.28 to 1.67)	219 per 1000	68 fewer per 1000 (from 157 fewer to 147 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Downgraded by 1 or 2 increments because of heterogeneity I^2=86%, p<0.00001, unexplained by subgroup analysis

Table 5: Clinical evidence summary: Lorazepam versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Lorazepam (95% CI)
Mortality: adults	137 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.49 (0.18 to 1.33)	155 per 1000	79 fewer per 1000 (from 127 fewer to 51 more)
Termination of SE at time of arrival at ED: adults	137 (1 study)	MODERATE[1] due to risk of bias	RR 2.8 (1.71 to 4.58)	211 per 1000	380 more per 1000 (from 150 more to 756 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 6: Clinical evidence summary: Lorazepam versus drugs (diazepam, levetiracetam, paraldehyde, phenobarbital or phenytoin)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Drug	Risk difference with Lorazepam (95% CI)
Mortality - vs diazepam: adults	134 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.72 (0.43 to 6.9)	44 per 1000	32 more per 1000 (from 25 fewer to 260 more)
Mortality - vs levetiracetam: adults	44 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.99 (0.5 to 1.94)	435 per 1000	4 fewer per 1000 (from 217 fewer to 409 more)
Mortality - vs paraldehyde: children	160 (1 study)	LOW[2] due to imprecision	RR 1.15 (0.59 to 2.27)	162 per 1000	24 more per 1000 (from 67 fewer to 206 more)
Termination of SE within 10 min- - vs diazepam: children	61 (1 study) 10 min	LOW[1,2] due to risk of bias, imprecision	RR 1.09 (0.77 to 1.54)	647 per 1000	58 more per 1000 (from 149 fewer to 349 more)

Termination of SE within 10 min- - vs paraldehyde: children	160 (1 study) 10 min	MODERATE[2] due to imprecision	RR 1.22 (0.99 to 1.52)	612 per 1000	135 more per 1000 (from 6 fewer to 318 more)
Termination of SE at time of arrival at ED - vs diazepam: adults	134 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.39 (0.99 to 1.95)	426 per 1000	166 more per 1000 (from 4 fewer to 405 more)
Termination of SE at time of arrival at ED - vs midazolam: adults and children	893 (1 study)	MODERATE[1] due to risk of bias	RR 0.86 (0.79 to 0.94)	734 per 1000	103 fewer per 1000 (from 44 fewer to 154 fewer)
Termination of SE within 30 mins - vs levetiracetam: adults	79 (1 study) 30 min	LOW[1] due to risk of bias	RR 0.99 (0.77 to 1.27)	763 per 1000	8 fewer per 1000 (from 176 fewer to 206 more)
Time to seizure cessation- vs midazolam: children	80 (1 study)	HIGH		The mean time to seizure cessation in the control groups was 92.69	The mean time to seizure cessation in the intervention groups was 1.57 lower (12.44 lower to 9.3 higher)
Seizure recurrence within 24 hours - vs diazepam: children	61 (1 study) 24 hours	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.63 (0.27 to 1.46)	353 per 1000	131 fewer per 1000 (from 258 fewer to 162 more)
Seizure recurrence within 24 hours - vs levetiracetam: adults	79 (1 study) 24 hours	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.54 (0.62 to 3.84)	158 per 1000	85 more per 1000 (from 60 fewer to 448 more)
Seizure recurrence within 24 hours - vs midazolam: adults	893 (1 study) 24 hours	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.93 (0.64 to 1.35)	114 per 1000	8 fewer per 1000 (from 41 fewer to 40 more)
Seizure recurrence within 24 hours - vs paraldehyde: children	160 (1 study) 24 hours	LOW[2] due to imprecision	RR 0.73 (0.31 to 1.71)	138 per 1000	37 fewer per 1000 (from 95 fewer to 98 more)

Seizure freedom at 24 hours - vs levetiracetam: adults	79 (1 study) 24 hours	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.85 (0.57 to 1.25)	605 per 1000	91 fewer per 1000 (from 260 fewer to 151 more)
Length of hospital stay (days) – vs midazolam: adults	536 (1 study)	MODERATE[1] due to risk of bias		The mean length of hospital stay (days) in the control groups was 6.7	The mean length of hospital stay (days) in the intervention groups was 1.2 lower (2.64 lower to 0.24 higher)
Length of ICU stay (days) - vs midazolam: adults	278 (1 study)	MODERATE[1] due to risk of bias		The mean length of ICU stay (days) in the control groups was 5.7	The mean length of ICU stay (days) in the intervention groups was 1.6 lower (3.43 lower to 0.23 higher)
Adverse events, respiratory failure - vs levetiracetam: adults	44 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 2.19 (0.89 to 5.37)	217 per 1000	259 more per 1000 (from 24 fewer to 950 more)
Adverse events, hypotension - vs diazepam: children	61 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.18 (0.02 to 1.37)	206 per 1000	169 fewer per 1000 (from 202 fewer to 76 more)
Adverse events, hypotension - vs levetiracetam: adults	44 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 4.38 (1.05 to 18.35)	87 per 1000	294 more per 1000 (from 4 more to 1000 more)
Adverse events, hypotension - vs phenobarbital: adults	260 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 0.77 (0.57 to 1.03)	460 per 1000	106 fewer per 1000 (from 198 fewer to 14 more)

Adverse events, hypotension - vs phenytoin: adults	263 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.07 (0.76 to 1.49)	331 per 1000	23 more per 1000 (from 79 fewer to 162 more)
Adverse events, hypotension - vs midazolam: adults and children	893 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.09 (0.5 to 2.36)	27 per 1000	2 more per 1000 (from 13 fewer to 36 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 7: Clinical evidence summary: Valproate versus phenytoin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Drug	Risk difference with Valproate (95% CI)
Termination of SE after drug infusion: children	68 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.55 (0.97 to 2.46)	424 per 1000	233 more per 1000 (from 13 fewer to 619 more)
Seizure recurrence within 24 hours: children	68 (1 study) 24 hours	LOW[1,2] due to risk of bias, imprecision	RR 0.44 (0.19 to 1.01)	394 per 1000	221 fewer per 1000 (from 319 fewer to 4 more)
Seizure freedom at 24 hours: children	68 (1 study) 24 hours	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.75 (0.34 to 1.68)	303 per 1000	76 fewer per 1000 (from 200 fewer to 206 more)
Adverse events, respiratory depression: children	37 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.3 (0.03 to 3.06)	143 per 1000	100 fewer per 1000 (from 139 fewer to 294 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 8: Clinical evidence summary: Phenytoin versus phenobarbital

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Phenobarbital	Risk difference with Phenytoin (95% CI)
Adverse events, hypotension	251 (1 study): adults	LOW[1,2] due to risk of bias, imprecision	RR 0.72 (0.53 to 0.98)	460 per 1000	129 fewer per 1000 (from 9 fewer to 216 fewer)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

See Appendix F: section F.1 for full GRADE tables.

1.2.6 Economic evidence

1.2.6.1 Included studies

Two health economic studies with relevant comparisons were included in this review: Both were different country perspectives comparing the branded buccal Midazolam product of Buccolam, with standard care (can vary depending on perspective), another buccal midazolam product, and rectal diazepam.[91,92]

These are summarised in the health economic evidence profiles below (**Table 9** and **Table 10**) and the health economic evidence tables in Appendix H: section H.1.

1.2.6.2 Excluded studies

One economic study relating to this review question was identified but was excluded due to not being the correct economic evaluation design. [19] This is listed in Appendix I:, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G: section G.1.

1.2.6.3 Summary of studies included in the economic evidence review

Table 9: Health economic evidence profile: Buccolam versus standard care, buccal midazolam, and rectal diazepam

Study	Applicability	Limitations	Other comments	Incremental cost [(c)]	Incremental effects	Cost effectiveness	Uncertainty
Lee 2013 [91] (Wales)	Partially applicable [(a)]	Potentially serious limitations[(b)]	• Probabilistic discrete event simulation and decision tree model based on single UK RCT (McIntyre 2005)[115] • Cost-utility analysis (QALYs) • Population: Paediatric patients with a diagnosis of epilepsy suffering prolonged, acute, convulsive seizures in the community setting. • Time horizon: 6 years, and also 1 year. • Comparators: 1) Standard care (95% buccal Midazolam, 5% rectal Diazepam) 2) Buccolam 3) Buccal Midazolam 4) Rectal Diazepam	(2−1): saves £2,939 (2−3): saves£886 (2−4): saves£14,269	(2−1): 0.025 (2−3): 0.013 (2−4): 0.082	Intervention 2 (Buccolam) dominates all other interventions.	Probability Buccolam cost effective (£20/£30K threshold): NR Probabilistic sensitivity analysis was performed with 10,000 Monte Carlo simulations. Scenario analyses undertaken include Varying the shelf life of buccal Midazolam to make it shorter, having more doses per bottle of buccal Midazolam, having two bottles of unlicensed buccal Midazolam ordered per prescription (instead of 1) which lowers the cost), and Buccolam/unlicensed buccal Midazolam are as effective as diazepam rather than more effective. All showed Buccolam would still be cost saving.

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial
(a) UK study (Wales), EQ-5D but filled in by clinicians not patients or their parents/carers.

(b) Costs out of date: Buccal Midazolam in particular based on current BNF costs this would be more expensive now because only comes in one pre-filled syringe. But costs depend on dose and how it is packaged (separate pre-filled multiple syringes or not) so uncertainty about cost effectiveness based on which buccal product is used as there are generic versions available which are not listed in the BNF. Funded by manufacturers. Most inputs elicited from surveys and are assumptions.
(c) Cost components incorporated: Drug costs, ambulance costs, hospital costs (inpatient admissions and ICU/HDU admissions).

Table 10: Health economic evidence profile: Buccolam versus standard care, buccal midazolam, and rectal diazepam

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Lee 2014[92] (Scotland)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Discrete event simulation and decision tree model based on single UK RCT (McIntyre 2005)[115] • Cost-utility analysis (QALYs) • Population: Paediatric patients with a diagnosis of epilepsy suffering prolonged, acute, convulsive seizures in the community setting. • Time horizon: 1 year. • Comparators: 1) Standard care (100% buccal Midazolam) 2) Buccolam 3) Buccal Midazolam 4) Rectal Diazepam *Note that 7 European perspectives were modelled, (Scotland, Wales, Germany, France, Spain, Italy, Switzerland). The Welsh perspective is included in the previous*	(Scottish perspective)[(c)] (2−1): saves £322 (2−3): saves £322 (2−4): saves £1,494	(Scottish perspective) (2−1): 0.00082 (2−3): 0.00082 (2−4): 0.00637	Intervention 2 (Buccolam) dominates all other interventions.	Unclear if probabilistic analysis undertaken. Upper and lower bounds of each parameter used in deterministic sensitivity analysis. The three most influential parameters on the results for the Scottish perspective were: • Probability carer doesn't administer treatment with buccal midazolam. • Probability carer doesn't administer treatment with Buccolam. • Probability of failed delivery of buccal midazolam.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			paper. The most relevant remaining perspective to the UK is the Scottish perspective and therefore is the only perspective extracted here.				

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial

(a) Has a UK perspective, and uses EQ-5D but filled in by clinicians not patients or their parents/carers.

(b) Costs out of date: Buccal Midazolam in particular based on current BNF costs this would be more expensive now because only comes in one pre-filled syringe. But costs depend on dose and how it is packaged (separate pre-filled multiple syringes or not) so uncertainty about cost effectiveness based on which buccal product is used as there are generic versions available which are not listed in the BNF. Funded by manufacturers. Most inputs elicited from surveys and are assumptions.

(c) 2012 Euros converted to 2012 UK pounds based on exchange rate reported in the paper (as costs were converted to Euros for country comparison in the paper).[146]. Cost components incorporated: Drug costs, ambulance costs, hospital costs (inpatient admissions and ICU/HDU admissions).

1.2.7 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.2.8 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness. The most commonly used drugs reported in the included clinical evidence are reported here for an illustration of unit costs.

Table 11: UK costs of drugs used for Status Epilepticus

Drug	Description	Cost	Dose	Cost per dose	Cost source
Lorazepam					
IV	4mg/ml 10 ampoules	£3.54	4mg	£0.35	BNF (NHS indicative price) (a)
Diazepam					
IV	10mg/2ml 10 ampoules	£5.50	10mg	£0.55	BNF (drug tariff price)
Rectal	10mg/2.5ml 5 tubes	£5.90	10mg	£1.48	BNF (drug tariff price)
Midazolam					
Buccal (Oromucosal solution) (b)	Buccolam (Midazolam hydrochloride): 10mg/2ml Pack of 4 pre-filled syringes	£91.50	10mg	£22.88	BNF (drug tariff price)
	Epistatus (Midazolam maleate): 10mg/ml 1 pre-filled syringe	£45.76	10mg	£45.76	BNF (drug tariff price)
Intranasal	Solution for infusion 50mg/50ml 1 vial	£9.56	10mg	£1.91	BNF (NHS indicative price) (c)

Source: BNF Drug Tariff price (NHS indicative price where drug tariff price isn't reported), 21/02/20[23].
Sources of doses from the review.
(a) No drug tariff price was available for this formulation
(b) There are only branded products available for this formulation on the BNF
(c) The lowest of two indicative prices for this dose.

Some types of administration may also require other resources like an IV line and solution to dilute the drug for infusion.

Equipment	Cost per person	Source
Intravenous administration		
1 x Cannula (Venflon)	£0.86	NHS Supply Chain 2018
2 x 10ml syringe	£0.45	
1 x syringe bung	£0.51	
1 x Cliniwipe Disinfectant Wipe	£0.02	
1 x IV dressing	£0.90	
1 x drawing up needle	£0.45	

Equipment	Cost per person	Source
1 x Sodium chloride 0.9%	£0.04	Electronic Market Information Tool (eMIT)
Total cost	**£3.23**	

Source: NHS supply chain[142] and Electronic Market Information Tool (eMIT)[45]

1.2.9 Evidence statements

1.2.9.1 Effectiveness/Qualitative

- None

1.2.9.2 Economic

- Two cost utility analyses found that Buccolam was dominant (less costly and more effective) compared to standard care, buccal midazolam, and rectal diazepam. This analysis was assessed as partially applicable with potentially serious limitations.

1.3 Review question: Add on

What antiepileptic drugs (add-on therapy) are effective in the treatment of status epilepticus?

1.3.1 Summary of the protocol

For full details, see the review protocol in Appendix A: section A.2.

Table 12: PICO characteristics of review question

Population	Inclusion: Children, young people and adults with status epilepticus (convulsive and non-convulsive) who are non-responsive to first line therapy. Strata: Convulsive status epilepticus Non-convulsive status epilepticus (focal vs myoclonic vs absence) Exclusion: New-born babies (under 28 days) with acute symptomatic seizures
Interventions	Brivaracetam Carbamazepine (for focal motor status) Chlormethiazole (clomethiazole) Clobazam Clonazepam (for myoclonic status) Chloral hydrate Diazepam Eslicarbazepine Fosphenytoin General anaesthetic induction agents Immunotherapy Intravenous immunoglobulin Lacosamide Levetiracetam Lorazepam Midazolam Oxcarbazepine Oxygen Paraldehyde Perampanel Phenobarbital (phenobarbitone) Phenytoin Rufinamide Stiripentol Steroids (methylprednisolone, prednisolone) Topiramate Valproate (sodium valproate / valproic acid) Zonisamide Dose according to prescriber discretion and / or local protocols
Comparisons	• One add-on drug vs monotherapy • One add-on drug vs different add-on drug • Add-on drug vs failure on initial therapeutic management (for example 2 drugs previously administered)
Outcomes	• mortality (including SUDEP)

	• time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive))
	• time to event seizure cessation
	• seizure recurrence greater than or less than 24 hours after administration of monotherapy
	• time to seizure recurrence after administration of monotherapy
	• quality of life (QOLIE-31, QOLIE-AD-48)
	• length of ICU stay
	• length of hospital stay
	• mean Glasgow outcome scale (% difference in the means between the two groups)
	• adverse events
	  ○ respiratory depression
	  ○ hypotension
	  ○ frequency of endotracheal intubation
	  ○ ICU admission
	  ○ Neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance
	• healthcare resource use

Study design	• RCTs • Systematic reviews of RCTs Exclusion: Non-English publications, non-randomised studies, conference abstracts It is anticipated that there will be sufficient RCT evidence that there is no need to search for non-randomised studies.

1.3.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.3.3 Effectiveness evidence

1.3.3.1 Included studies

Twenty one studies and three supplemental studies (that report from the same trials) were included in the review;[4, 8, 37, 42, 43, 46, 47, 55, 63, 65, 75, 106, 107, 111, 113, 120, 122, 144, 179, 192, 205, 233, 238] these are summarised in Table 2. Studies were identified in both children and adult populations. Subgroup analysis by age was only conducted where there was evidence of heterogeneity. This occurred for one outcome comparing sodium valproate and phenobarbital[111,205]Evidence from these studies is summarised in the clinical evidence summary below (Table 3). All studies were on convulsive status epilepticus (SE). They were all in epilepsy populations that had previously failed to stabilise on a benzodiazepine. The majority of the studies were conducted in the emergency department (ED)

See also the study selection flow chart in Appendix C: section C.2 study evidence tables in Appendix D: section D.2, forest plots in Appendix E: section E.2 and GRADE tables in Appendix F: section F.2.

1.3.3.2 Excluded studies

See the excluded studies list in Appendix I:

1.3.4 Summary of clinical studies included in the evidence review

Table 13: Summary of studies included in the evidence review

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
Agarwal 2007[4] India	Intravenous valproic acid: 20 mg/kg as loading dose at a rate of 40 mg/min n=50	Intravenous phenytoin: 20 mg/kg at 2 mg/min n=50	Adults Age: mean (SD) Valproic acid: 27.4 (16.8) years Antiepileptic drug withdrawal / noncompliance: 24% Inflammatory granuloma (neurocysticercosis / tuberculoma: 24% CNS infection: 20% Age: mean (SD) Phenytoin: 27 (15.1) years Antiepileptic drug withdrawal / noncompliance: 28% Inflammatory granuloma (neurocysticercosis / tuberculoma: 24% CNS infection: 24%	Mortality at 7 days Cessation of SE within 20 min Seizure recurrence within 24 hours Hypotension Respiratory depression	ED/ICU All patients given intravenous diazepam in doses of 0.2 mg/kg at 2 mg/min up to a maximum of 20 mg before being labelled as refractory
Amir-Nikpour 2018[8]	Intravenous sodium valproate:	Intravenous phenytoin: 20 mg as loading dose	Adults Age: mean (SD)	Mortality at 7 days	ED

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
Iran	30 mg/kg as the loading dose then 4-8 mg/kg every 8 hours as maintenance therapy n=55	at 2 mg/min up to a maximum of 20 mg n=55	Sodium valproate: 42.16 (15.94) years Drug withdrawal: 35% Primary generalised seizures: 18% Brain stroke: 15% Age: mean (SD) Phenytoin: 43.69 (17.60) years Drug withdrawal: 33% Primary generalised seizures: 18% Brain stroke: 13%	Cessation of SE within 7 days Hypotension	All patients had been treated with intravenous diazepam in doses of 0.2 mg/kg at 2mg/min up to a maximum of 20 mg before being labelled as refractory
Chakravarthi 2015[36, 37] India	Intravenous levetiracetam: loading dose of 20 mg/kg at a rate of 100 mg/min n=22	Intravenous phenytoin: 20 mg at a maximum rate of 50 mg/min n=22	Adults Age: mean (SD) 35.41 (16.03) years Levetiracetam Remote symptomatic: 55% Idiopathic: 32% Acute symptomatic: 14% Phenytoin Remote symptomatic: 45%	Mortality during hospital stay (no further details given) Cessation of SE within 30 min Mean duration of SE of good responders Recurrence of seizure within 24 hours Good outcome at discharge: functional independence measure Length of hospital stay	ED All patients had been treated with intravenous lorazepam 0.1 mg/kg at 1 mg/min before being labelled as refractory

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
			Idiopathic: 27% Acute symptomatic: 27%		
Chen 2011[42] China	Intravenous sodium valproate: initial bolus of 30 mg/kg at a rate of 6 mg/kg/hour as maintenance dose follows by a continuous infusion at a rate of 1-2 mg/kg per hour, infusion maintained for at least 6 hours after the control of last seizure then gradually tapered over 24 hours n=30	Intravenous diazepam (3rd dose): initial bolus of 0.2 mg/kg at a rate of 5 mg/min followed by a continuous infusion at a rate of 4 mg per hour, rate was maintained for 3 min then decreased every 3 min by 1 µg/kg/min until seizures were controlled or a maximum duration of 1 hour n=36	Young adults and adults Age: mean (SD) 41 (21) years Valproate Epilepsy related: 33% Viral encephalitis: 40% CVD: 17% Diazepam Epilepsy related: 36% Viral encephalitis: 28% CVD: 14%	Mortality at hospital discharge (no further details given) Cessation of SE within 1 hour and no recurrence within 6 hours Recurrence of seizure within 24 hours Hypotension Need for intubation	ED All patients had been treated with intravenous diazepam 0.2 mg/kg twice in a 10 min period
Chitsaz 2013[43] Iran	Intravenous sodium valproate: initial bolus of 20 mg/kg infused within 10 min, and half an hour after this loading, continuous infusion at a rate of 1 mg/kg/hour as maintenance dose within 24 hours n=15	Intravenous phenytoin: initial bolus of 20 mg/kg and at a rate of 50 mg/min (25 mg/min for older patients), then maintenance dose of 4.5 mg/kg/h for 24 hours n=15	Young adults and adults Age: mean (SD) 46.5 (18.7) years Patients had intractable epilepsy	Cessation of SE within 12 hours	ED All patients had been treated with intravenous diazepam in doses of 0.15 mg/kg at 5 mg/min, if seizure remained uncontrolled at 1 min, then diazepam was administered again, if seizure remained patients were labelled as refractory
ConSEPT 2009[46, 47]	Intravenous/intraosseous phenytoin: 20 mg/kg	Intravenous/intra-osseous levetiracetam:	Children Age: mean (SD)	Mortality at 3 months	ED

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
Australia New Zealand	infusion over 20 min (50 mg/ml phenytoin; 0.9% sodium chloride to a maximum volume of 20 ml) n=114	40 mg/kg infusion over 20 min (maximum 1 g, diluted 1.4 with 0.9% sodium chloride to a maximum of 20 ml) n=119	3.9 (3.8) years Phenytoin Febrile: 72% Focal onset:12% Levetiracetam Febrile: 73% Focal onset:12%	Cessation of seizure within 5 min Cessation of seizure within 2 hours	All patients initially treated 2 doses of benzodiazepines
ESSET 2019[75] USA	Intravenous fosphenytoin: weight-based infusion rate provided fosphenytoin at a dose of 20 mgPE per kilogram (maximum, 1500 mgPE) n=118	Intravenous levetiracetam: weight-based infusion rate provided levetiracetam at a dose of 60 mg per kilogram (maximum, 4500 mg) n=145 Intravenous valproate: weight-based infusion rate provided valproate at a dose of 40 mg per kilogram (maximum, 3000 mg) n=121	Adults and children Age: mean (SD) Fosphenytoin: 32.8 (25.4) years Seizure or status epilepticus: 88.1% Non-epileptic spell: 9.3% Unable to adjudicate: 2.5% Age: mean (SD) Levetiracetam: 33.3 (26) years Seizure or status epilepticus: 88.3% Non-epileptic spell: 9.0%	Mortality at end of participation in trial (no further details given) Cessation of SE within 1 hour Seizure recurrence within 24 hours ICU admission Hypotension	57 EDs All patients were refractory to generally accepted cumulative dose of benzodiazepines for seizures lasting more than 5 min, and continued to have persistent or recurrent convulsions in the ED at least 5 min after the last dose of benzodiazepine (to provide sufficient time for the drug at this dose to act) and no more than 30 min after the last dose of benzodiazepine. The minimal adequate cumulative doses of benzodiazepines were defined as diazepam at a

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
			Unable to adjudicate: 2.8% Age: mean (SD) Valproate: 32.2 (25.4) years Seizure or status epilepticus: 84.3% Non-epileptic spell: 10.7% Unable to adjudicate: 5.0%		dose of 10 mg (administered intravenously or rectally), lorazepam at a dose of 4 mg (administered intravenously), or midazolam at a dose of 10 mg (administered intravenously or intramuscularly) for all adults and for children with a body weight of at least 32 kg; and diazepam at a dose of 0.3 mg of body weight/kg (administered intravenously or rectally), lorazepam at a dose of 0.1 mg/kg (administered intravenously), or midazolam at a dose of 0.3 mg/kg (administered intramuscularly) or 0.2 mg/kg (administered intravenously) for children who weighed less than 32 kg, these drugs may have been administered in divided doses, including before the patient's arrival in the ED
Fallah 2007[55]	Intravenous lignocaine:	Intravenous midazolam:	Children Age: mean (range)	Cessation of SE Length of ICU stay	ICU

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
Iran	initial dose of 1 mg/kg intravenously at a rate of 25 mg/min, a second bolus of 1 mg/kg was infused if no response or seizure recurred, if seizures did not stop after 2nd dose and within 15 min, continuous lignocaine infusion of 1 mg/kg/hour, if still ineffective, lignocaine was infused with the same dose and then decreased by 0.5 mg/kg every hour until cessation n=10	initial bolus of 0.15 mg/kg followed by continuous intravenous infusion of 1 µg/kg/min, with an increase of 1 µg/kg/min every 15 min until control of seizure or maximum dose 6 µg/kg/min was reached, if drug was ineffective at controlling the seizure, it was infused at the same dose for 24 hours, then decreased by 1 µg/kg/min every 2 hours until cessation n=10	3.8 (0.1 to 12) years) Lignocaine Symptomatic epilepsy: 80%, idiopathic epilepsy: 20% Midazolam Symptomatic epilepsy: 90%, idiopathic epilepsy: 10%		All patients initially treated with a bolus of intravenous diazepam (0.2 to 0.3 mg/kg) which was repeated after 5 if seizure reoccurred, this was followed by phenytoin (15 to 20 mg/kg over 20 min, if seizures continued, phenobarbitone (10 mg/kg) was intravenously administered over 20 min, if seizure recurred patients were labelled as refractory
Gujjar 2017[63] Oman	Intravenous levetiracetam: 30 mg/kg over 30 min Maintenance treatment of 1 to 1.5 g bid, starting 12 hours after first dose n=22	Intravenous phenytoin: 20 mg/kg at a maximum rate of 50 mg/min Maintenance treatment of 300 mg/day 24 after initial dose n=30	Adults Age: mean (SD) 37.8 (18) years Levetiracetam Epilepsy: 50% Remote symptoms: 36%: Acute symptoms: 14% Phenytoin Epilepsy: 60% Remote symptoms: 27% Acute symptoms: 17%	Mortality during hospital stay (no further details given) Cessation of SE within 24 hours Good outcome at discharge mRS score Hypotension	ED/high-dependence unit/ICU All patients received lorazepam (4 mg) or diazepam (5-10 mg) over 2 min, if seizure persisted patients were labelled as refractory

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
ECLIPSE 2019[106, 107] UK	Intravenous levetiracetam: administered over 5 min in a dose of 40 mg/kg (maximum dose 2·5 g) n=212	Intravenous phenytoin: administered over a minimum of 20 min in a dose of 20 mg/kg (maximum dose 2 g and with a maximum infusion rate of 1 mg/kg per min) n=192	Children Age: median (IQR) Levetiracetam: 7 (1.3 to 5.9) years Febrile convulsion: 41% Seizure (pre-existing epilepsy): 30% First afebrile seizure: 11% Age: median (IQR) Phenytoin: 2.7 (1.6 to 5.6) years Febrile convulsion: 43% Seizure (pre-existing epilepsy): 34% First afebrile seizure: 9%	Mortality at 14 days Admission to critical care Confusion Hypotension	ED Inclusion stated children that required second line treatment were eligible
Handral 2020 [65]	Levetiracetam: intravenous Levetiracetam 30 mg/kg over 10 min. n=58	Fosphenytoin: Fosphenytoin infusion 30 mg/kg over 20 min. n=58	Children Age - Mean (SD): LEV: 3.09+2.98; FHP: 3.77+3.79. LEV: Generalized 75.9% Partial seizures: 24.1%	Cessation of seizure from 10 – 20 minutes Seizure recurrence in 48 hours Bradycardia Tracheal intubation	emergency department in a tertiary care hospital The study group included all the children who presented with SE in the age group from 1 month to 18 years and did not respond to two doses of

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
			FHP: Generalized seizures: 81% Partial: 19%		lorazepam 0.1 mg/kg/dose.
Malamiri 2012[111] Iran	Intravenous sodium valproate given at loading dose of 20 mg/kg, diluted in 20 ml saline, at a maximum rate of 5-6 mg/kg per minute over 5-10 min via an infusion pump, the sodium maintenance dose was continuous infusion pf 1 mg/kg per hour, given 60 min after the bolus dose n=30	Intravenous Phenobarbital: given at a loading dose of 20 mg/kg via an infusion pump at a rate not faster than 60-100 mg/min. n=30	Children Age: median (range) Sodium valproate: 5 (3 to 16) years Remote symptomatic epilepsy: 70% Idiopathic epilepsy: 13% Prolonged febrile seizures: 17% Age: median (range) Phenobarbital: 4 (3 to 11) years Prolonged febrile seizures: 34% Idiopathic epilepsy: 23% Remote symptomatic epilepsy: 43%	Seizure control within 20 min Recurrence of seizure within 24 hours Hypotension Transient depressed respiration	Two major university paediatric hospitals All patients whose seizures were not controlled by a bolus of IV diazepam (0.2 mg/kg) within 5 min
Masapu 2018[113] India	Propofol: started at a plasma concentration of 1.0 µg/ml and escalated	Midazolam: administered as a bolus of 0.05 mg/kg followed by an infusion	Adults Age: mean (range)	Mortality during therapy Cessation of SE for 48 hours Hypotension	ED All patients unresponsive to the first line IV lorazepam

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
	based on seizure response n=12	n=12	Propofol: 49 (30 to 65) years Generalised tonic-clonic seizures: 45.5% Complex partial seizures: 55.5% Age: mean (range) Midazolam: 45 (26.75 to 48.5) years Generalised tonic-clonic seizures: 25% Complex partial seizures: 66.7%		(0.1 mg/kg) and any two of the second-line IV anti-epileptic drugs (phenytoin [15 mg/kg], valproate [20–25 mg/kg], and levetiracetam [30 mg/kg]) were included in the study
Mehta 2007[120] India	Valproate: given as an initial loading bolus of 30 mg/kg diluted 1:1 in normal saline from 2 to 5 min n=20	Diazepam: infusion was started at a rate of 10 µg/kg/min and was increased every 5 min by 10 µg/kg/min until status was controlled or a maximum dose of 100 µg/kg/min was reached n=20	Children Age: mean (SD) Valproate: 36.3 (32.8) months Meningoencephalitis: 45% Pyogenic meningitis: 5% Central nervous system (tuberculosis): 5% Epilepsy: 15% Intracranial bleeding; 10% Metabolic disorder: 5% Others: 15%	Cessation of SE within 30 min Time for seizure cessation after drug administration ICU admission Hypotension Respiratory depression	Emergency and Neurology wards of the Advanced Paediatric Centre Patients in whom seizures were not controlled after a bolus of diazepam (0.2 mg/kg) followed by phenytoin (20 mg/kg in normal saline infusion) and a repeat dose of phenytoin (5 to 10 mg/kg in normal saline infusion) 10 min after the first dose were considered to have refractory status epilepticus

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
			Age: mean (SD) Diazepam: 44.5 (42.8) months Meningoencephalitis: 55% Pyogenic meningitis: 15% Central nervous system (tuberculosis): 5% Epilepsy: 5% Intracranial bleeding: 5% Metabolic disorder: 5% Others: 10%		
Misra 2017[122] India	Valproate: 30 mg/kg was administered intravenously at a rate of 100 mg/min. n=33	Lacosamide: 400 mg intravenously was administered at a rate of 60 mg/min. n=33	Adults Age: median (range) Valproate: 40 (18 to 85) years CNS infection: 33.3% Stroke: 18.2% Others: 48.5% Age: median (range) Lacosamide: 40 (18 to 90) years CNS infection: 33.3% Stroke: 30.3% Others: 36.4%	Time for seizure cessation after drug Cessation of SE for 1 hour Seizure freedom within 24 hours	Tertiary care teaching hospital Patients received 4 mg lorazepam IV in 10 ml saline in 2 to 4 min, which was repeated after 10 min if seizures were not controlled, those who did not respond to second dose of lorazepam were then randomised

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
Noureen 2019[144]	Levetiracetam: a dose of 40 mg/kg (maximum of 500 mg) infused over 15 minutes. The medication was diluted in normal saline. Supportive treatment (e.g., antipyretics and antibiotics) was provided simultaneously to both groups according to the hospital protocol. n=300	Phenytoin: dose was 20 mg/kg (maximum of 250 mg) given over 30 minutes. The medication was diluted in normal saline. Supportive treatment (e.g., antipyretics and antibiotics) was provided simultaneously to both groups according to the hospital protocol. n=300	Children Age: LEV: 3.52±0.24; PHT: 3.46±0.22 Levetiracetam: Meningitis: 40% Cerebral palsy & epilepsy: 20% Epilepsy:17% Phenytoin: Meningitis/encephalitis: 43% Cerebral palsy & epilepsy: 19% Epilepsy: 17%	Time to seizure cessation Cardiac depression Respiratory depression	Emergency Department Patients with generalized CSE who did not responding to two doses of diazepam (0.2 mg/kg to a maximum of 10 mg, administered 5 minutes apart) were included in the study at 5 minutes after the second dose of diazepam.
Singhi 2002[192] India	Midazolam: given a bolus of 0.2 mg/kg followed by a continuous intravenous infusion starting at 2.0 µg/kg until control of the seizure or up to a maximum of 10.0µg/kg/min n=21	Diazepam: the infusion was started at a rate of 0.01 mg/kg/min and was increased every 5 min at a rate of 0.01 mg/kg/min until the seizure was controlled or the maximum dose of 0.1 mg/kg/min was reached n=19	Children Age: mean (SD) Midazolam: 40.6 (44.3) months Meningoencephalitis: 33% Bacterial meningitis: 14% Late haemorrhagic disease of newborn:19%	Mortality (follow-up not given) Time to initial and final seizure cessation Cessation of SE within 6 hours Seizure recurrence whilst on infusion and after stopping infusion Hypotension	Emergency and Intensive Care Services of the Advance Paediatric Centre Patients whose seizures were not controlled after two bolus doses of diazepam (0.3 mg/kg) and phenytoin infusion (20 mg/kg in normal saline infusion over 20 min) followed by a repeat dose of benzodiazepine were considered to have refractory status epilepticus

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
			Age: mean (SD) Diazepam: 49.6 (43.3) months Meningoencephalitis: 53% Bacterial meningitis: 16% Late haemorrhagic disease of new-born: 0%		
Senthil-Kumar 2018[179]	Levetiracetam: 30mg/kg of LEV infusion over 7 minutes diluted 1:1 with 0.9% sodium chloride to a minimum volume of 10ml. Duration administered over 7 minutes. n=25	Intervention 2: Drug - Fosphenytoin. 20mg/kg PE of FPHT diluted 1 in 4 with 0.9% sodium chloride to a minimum volume of 20ml. Duration administered over 7 minutes. n=25	Children Age: mean (SD): Levetiracetam: 2.28 + 2.19. Fosphenytoin: 3.34 + 3.36 Levetiracetam: focal seizures: 4%. GTCS: 96% Fosphenytoin: Focal seizures: 4%. GTCS: 96%	Cessation of seizure within 5 minutes Time taken for seizure cessation Length of PICU stay Length of hospital stay Respiratory depression	Paediatric emergency Department Children with convulsive status epilepticus and who were still seizing after two doses of benzodiazepines (diazepam/ lorazepam/ midazolam) administered by one of the following route (rectal/ buccal/ intranasal/ intravenous/intramuscular) at the recommended dose were included in the study
Su 2016[205] China	Phenobarbital: a loading dose of 20 mg/kg (an additional 5–10 mg/kg may be administered) began at a rate of 50 mg/min, followed by an	Valproate: a loading dose of 30 mg/kg (an additional 15 mg/kg may be administered) began at a rate of 3 mg/kg/min, followed by a continuous infusion at	Adults Age: mean (SD) 41.72 (17.14) years Phenobarbital Epilepsy related: 38%	Mortality at 3 months Recurrence of seizure within 24 hours Hypotension Transient depressed respiration	Emergency room or neurocritical care unit Patients who had not responded to first-line anticonvulsants were enrolled in this trial and

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
	intravenous dose of 100 mg every 6 hours n=37	a rate of 1–2 mg/kg/hour n=36	Virus encephalitis: 38% Cerebrovascular disease: 8% Valproate Epilepsy related: 25% Virus encephalitis: 44% Cerebrovascular disease: 8%		were randomized to receive either intravenous phenobarbital or valproate
Vignesh 2020[233]	Levetiracetam: injection levetiracetam (Levesam, 5 mL per 500 mg, Abbott Ind. Ltd, India) was at a concentration of 5 mg/mL in 0.9% normal saline dilution in the syringe. Patients not responding to intravenous lorazepam received the study drug at the dose of 20 mg kg over 20 minutes as an intravenous infusion. n=32	Phenytoin: phenytoin sodium (Ciroton, 2 mL per 100 mg, Ciron Pharmaceuticals, India) was prepared at a concentration of 5 mg/mL in 0.9% normal saline dilution in the syringe. Patients not responding to intravenous lorazepam received the study drug at the dose of 20 mg/kg over 20 minutes as an intravenous infusion n=35 Valproate (sodium valproate / valproic acid): injection sodium valproate (Valprol, 5 ml per 500 mg, Intas Pharmaceuticals, India) was prepared at a concentration of 5	Children Age - Mean (SD): (months) LEV: 58(50). PHT: 44(43). VAL: 59(44). Levetiracetam: Acute:44% Unknown:34% Remote 16% Phenytoin: Acute: 46% Remote:25% Unknown:20% Valproate: Unknown: 48% Acute:20% Remote:20%	Mortality Time to seizure cessation Length of ICU stay Length of hospital stay	Paediatric emergency room Children with convulsive status epilepticus (clonic, tonic, tonic-clonic, and myoclonic, focal or generalized) not responding to lorazepam were enrolled.

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
		mg/ml in 0.9% normal saline dilution in the syringe. Patients not responding to intravenous lorazepam received the study drug at the dose of 20 mg kg over 20 minutes as an intravenous infusion. n=35			
Wani 2019[238]	Levetiracetam: Children in this group 1 were given levetiracetam at a dose of 40 mg/kg diluted in 50 mL of normal saline over 10 min followed by a maintenance dose of 20 mg/kg/day to be given in two divided doses 12 h after initial dose. If seizures recurred after the first loading of the drug, a further additional dose of 10 mg/kg of the same drug was given. If seizures still recurred, the patients were loaded with valproate with a dose of 20 mg/kg dissolved in 50 ml of normal saline over 10 min and further a maintenance dose of 20 mg/kg in two divided doses was given.	Phenytoin: Children in the Phenytoin group were given IV phenytoin as 20 mg/kg diluted in normal saline over 20 min. If seizures recurred after the first loading of the drug, a further additional dose of 10 mg/kg of the same drug was given. If seizures still recurred, the patients were loaded with valproate with a dose of 20 mg/kg dissolved in 50 ml of normal saline over 10 min and further a maintenance dose of 20 mg/kg in two divided dose was given n=52	Children Age - Mean (SD): LEV:3.39 ± 3.32. PHT: 4.80 ± 4.11.	Time to seizure cessation Seizure recurrence	Tertiary Medical Centre Children who came with active seizures were given midazolam at a dose of 0.1 mg/kg slowly followed by IV levetiracetam and phenytoin depending on group allotment. Children with a history of status epilepticus and presently not in active seizure were given only levetiracetam or phenytoin. The subjects were randomized to receive either IV levetiracetam or IV phenytoin.

Study	Intervention	Comparison	Population: Age Top 3 reasons for SE	Outcomes	Comments
	n=52				

See Appendix D: section D.2 for full evidence tables.

1.3.5 Quality assessment of clinical studies included in the evidence review

Table 14: Clinical evidence summary: Sodium valproate versus phenytoin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Phenytoin	Risk difference with Valproate (95% CI)
Mortality	280 (3 studies)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.09 (0.51 to 2.32)	79 per 1000	7 more per 1000 (from 39 fewer to 104 more)
Cessation of SE within 15 minutes	70 (1 study)	⨁⨁⨁⊖ MODERATE2 due to imprecision	RR 0.94 (0.77 to 1.13)	886 per 1000	53 fewer per 1000 (from 204 fewer to 115 more)
Cessation of SE within 20 min	100 (1 study)	⨁⨁⨁⊖ MODERATE1 due to risk of bias	RR 1.05 (0.89 to 1.23)	840 per 1000	42 more per 1000 (from 92 fewer to 193 more)
Cessation of SE within 12 hours	30 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.22 (0.73 to 2.04)	600 per 1000	132 more per 1000 (from 162 fewer to 624 more)
Cessation of SE within 7 days	110 (1 study)	⨁⨁⊖⊖ LOW1,2	RR 1.1 (0.89 to 1.37)	709 per 1000	71 more per 1000 (from 78 fewer to 262 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Phenytoin	Risk difference with Valproate (95% CI)
		due to risk of bias, imprecision			
Time to seizure cessation (minutes)	70 (1 study)	⨁⨁⨁⨀ MODERATE2 due to imprecision		The mean time to seizure cessation (minutes) in the control groups was 1.4 minutes	The mean time to seizure cessation (minutes) in the intervention groups was 0.20 lower (0.81 lower to 0.41 higher)
Seizure recurrence within 24 hours	100 (1 study)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 0.75 (0.28 to 2)	160 per 1000	40 fewer per 1000 (from 115 fewer to 160 more)
PICU admission (days)	70 (1 study)	⨁⨁⨁⨁ HIGH		The mean PICU admission (days) in the control groups was 4 days	The mean PICU admission (days) in the intervention groups was 6.0 higher (4.31 to 7.69 higher)
Length of stay (days)	70 (1 study)	⨁⨁⨁⨀ MODERATE2 due to imprecision		The mean length of stay (days) in the control groups was 6.1 days	The mean length of stay (days) in the intervention groups was 0.60 lower (2.85 lower to 1.65 higher)
Hypotension	210 (2 studies)	⨁⨁⨁⨀ MODERATE1 due to risk of bias	Peto OR 0.12 (0.03 to 0.47)	86 per 1000	90 fewer per 1000 (from 140 fewer to 30 fewer)
Respiratory depression	100 (1 study)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 0.13 (0.01 to 2.15)	40 per 1000	40 fewer per 1000 (from 110 fewer to 30 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1 **Table 15: Clinical evidence summary: Levetiracetam versus phenytoin**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Phenytoin	Risk difference with Levetiracetam (95% CI)
Mortality	681 (5 studies)	⨁⨁⨀⨀ LOW1 due to imprecision	Peto OR 0.78 (0.24 to 2.52)	21 per 1000	0 fewer per 1000 (from 30 fewer to 20 more)
Cessation of SE within 5 min	337 (2 studies)	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 0.88 (0.74 to 1.05)	627 per 1000	75 fewer per 1000 (from 163 fewer to 31 more)
Cessation of SE within 5 - 20 minutes	104 (1 study)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 1.13 (0.64 to 2.02)	288 per 1000	37 more per 1000 (from 104 fewer to 294 more)
Cessation of SE within 15 minutes	67 (1 study)	⨁⨁⨁⨁ HIGH	RR 1.06 (0.91 to 1.23)	886 per 1000	53 more per 1000 (from 80 fewer to 204 more)
Cessation of SE within 20 - 40 minutes	104 (1 study)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 1 (0.06 to 15.57)	19 per 1000	0 fewer per 1000 (from 18 fewer to 280 more)
Cessation of SE within 30 min	644 (2 studies)	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 1.10 (1.03 to 1.17)	823 per 1000	82 more per 1000 (from 25 more to 140 more)
Cessation of SE within 2 h	233 (1 study)	⨁⨁⨁⨀ MODERATE1 due to imprecision	RR 0.94 (0.74 to 1.2)	544 per 1000	33 fewer per 1000 (from 141 fewer to 109 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Phenytoin	Risk difference with Levetiracetam (95% CI)
Cessation of SE within 24 h	52 (1 study)	⨁⨁⨁⨀ MODERATE1 due to imprecision	RR 1.17 (0.86 to 1.59)	700 per 1000	119 more per 1000 (from 98 fewer to 413 more)
Recurrence of seizure within 24 h	148 (2 studies)	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 0.46 (0.24 to 0.87)	324 per 1000	175 fewer per 1000 (from 42 fewer to 246 fewer)
Time to seizure cessation	67 (1 study)	⨁⨁⨁⨀ MODERATE1 due to imprecision		The mean time to seizure cessation in the control groups was 3 minutes	The mean time to seizure cessation in the intervention groups was 0.10 higher (0.5 lower to 0.7 higher)
Mean duration of SE of good responders	28 (1 study)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision			The mean duration of se of good responders in the intervention groups was 2.2 higher (19.36 lower to 23.76 higher)
Good outcome at discharge (FIM score)	44 (1 study)	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 1.06 (0.82 to 1.37)	818 per 1000	49 more per 1000 (from 147 fewer to 303 more)
Good outcome at discharge (mRS score)	52 (1 study)	⨁⨁⨀⨀ LOW2 due to imprecision	RR 1.36 (0.76 to 2.44)	400 per 1000	144 more per 1000 (from 96 fewer to 576 more)
Mean length of hospital stay (days)	111 (2 studies)	⨁⨁⨁⨀ MODERATE2 due to risk of bias		The mean length of hospital stay (days) in the control groups was 3.8 days	The mean length of hospital stay (days) in the intervention groups was 0.29 higher (0.46 lower to 1.05 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Phenytoin	Risk difference with Levetiracetam (95% CI)
Mean length of PICU admission (days)	67 (1 study)	⨁⨁⨁⨀ MODERATE1 due to imprecision		The mean length of PICU admission (days) in the control groups was 4 days	The mean length of PICU admission (days) in the intervention groups was 2.0 higher (0.49 to 3.51 higher)
Admission to critical care	286 (1 study)	⨁⨁⨀⨀ LOW2 due to risk of bias, imprecision	RR 1.19 (0.97 to 1.45)	537 per 1000	102 more per 1000 (from 16 fewer to 242 more)
Hypotension	314 (2 studies)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 0.67 (0.16 to 2.73)	31 per 1000	10 fewer per 1000 (from 26 fewer to 54 more)
Adverse events, confusion	262 (1 study)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	OR 7.28 (0.14 to 366.83)	0 per 1000	10 more per 1000 (from 10 fewer to 30 more)
Cardiac Depression	600 (1 study)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	Peto 0.13 (0.01 to 2.16)	7 per 1000	6 fewer per 1000 (from 7 fewer to 8 more)
Respiratory Depression	600 (1 study)	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 0.08 (0 to 1.36)	20 per 1000	18 fewer per 1000 (from 20 fewer to 7 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Table 16: Clinical evidence summary: Lignocaine versus midazolam

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Midazolam	Risk difference with Lignocaine (95% CI)
Cessation of SE: children	20 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 2.5 (0.63 to 10)	200 per 1000	300 more per 1000 (from 74 fewer to 1000 more)
Length of ICU stay: children	20 (1 study)	MODERATE[1] due to risk of bias			The mean length of ICU stay in the intervention groups was 4.6 lower (8.4 to 0.8 lower)
Intubation needing mechanical ventilation: children	20 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 0.29 (0.08 to 1.05)	700 per 1000	497 fewer per 1000 (from 644 fewer to 35 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 17: Clinical evidence summary: Sodium valproate versus lacosamide

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lacosamide	Risk difference with Valproate (95% CI)
Mortality: adults	66 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.2 (0.6 to 2.38)	303 per 1000	61 more per 1000 (from 121 fewer to 418 more)
Time for seizure cessation after drug administration (min) : adults	66 (1 study)	LOW[1,2] due to risk of			The mean time for seizure cessation after drug administration (min) in the

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Lacosamide	Risk difference with Valproate (95% CI)
		bias, imprecision			intervention groups was 0.61 lower (1.81 lower to 0.59 higher)
Cessation of SE for 1 hour: adults	66 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.1 (0.78 to 1.54)	636 per 1000	64 more per 1000 (from 140 fewer to 344 more)
Seizure freedom within 24 hours: adults	66 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.33 (0.84 to 2.12)	455 per 1000	150 more per 1000 (from 73 fewer to 509 more)
Hypotension: adults	66 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.14 (0 to 6.82)	30 per 1000	30 fewer per 1000 (from 110 fewer to 50 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 18: Clinical evidence summary: Midazolam versus diazepam

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Diazepam	Risk difference with Midazolam (95% CI)
Mortality: children	40 (1 study)	LOW[1] due to imprecision	RR 3.62 (0.87 to 14.97)	105 per 1000	276 more per 1000 (from 14 fewer to 1000 more)
Time to initial seizure cessation (min): children	40 (1 study)	MODERATE[1] due to imprecision			The mean time to initial seizure cessation (min) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Diazepam	Risk difference with Midazolam (95% CI)
					0.1 higher (7.04 lower to 7.24 higher)
Time to final seizure cessation (min): children	40 (1 study)	MODERATE[1] due to imprecision			The mean time to final seizure cessation (min) in the intervention groups was 81 higher (25.04 lower to 187.04 higher)
Cessation of SE within 12 hours (6 hours): children	40 (1 study)	MODERATE[1] due to imprecision	RR 0.96 (0.76 to 1.21)	895 per 1000	36 fewer per 1000 (from 215 fewer to 188 more)
Seizure recurrence whilst on infusion: children	40 (1 study)	MODERATE[1] due to imprecision	RR 3.62 (1.2 to 10.9)	158 per 1000	414 more per 1000 (from 32 more to 1000 more)
Seizure recurrence after stopping infusion: children	40 (1 study)	LOW[1] due to imprecision	RR 1.21 (0.31 to 4.71)	158 per 1000	33 more per 1000 (from 109 fewer to 586 more)
Hypotension: children	40 (1 study)	LOW[1] due to imprecision	RR 0.8 (0.39 to 1.66)	474 per 1000	95 fewer per 1000 (from 289 fewer to 313 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 19: Clinical evidence summary: Propofol versus midazolam

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Midazolam	Risk difference with Propofol (95% CI)
Mortality: adults	23 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.25 (0.68 to 2.27)	583 per 1000	146 more per 1000 (from 187 fewer to 741 more)

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Midazolam	Risk difference with Propofol (95% CI)
Cessation of SE for 48 hours: adults	23 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.82 (0.56 to 5.88)	250 per 1000	205 more per 1000 (from 110 fewer to 1000 more)
Hypotension: adults	23 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 3.27 (0.4 to 27)	83 per 1000	189 more per 1000 (from 50 fewer to 1000 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 20: Clinical evidence summary: Phenobarbital versus sodium valproate

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Valproate	Risk difference with Phenobarbital (95% CI)
Mortality: adults	73 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.53 (0.22 to 1.28)	306 per 1000	144 fewer per 1000 (from 238 fewer to 86 more)
Seizure control within 20 min: children	60 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 0.85 (0.68 to 1.07)	900 per 1000	135 fewer per 1000 (from 288 fewer to 63 more)
Recurrence of seizure within 24 hours: adults	50 (1 study)	MODERATE[1,2] due to risk of bias	RR 3.52 (1.31 to 9.44)	148 per 1000	373 more per 1000 (from 46 more to 1000 more)
Recurrence of seizure within 24 hours: adults	46 (2 studies)	LOW[1,2] due to risk of bias, imprecision	RR 0.21 (0.05 to 0.98)	312 per 1000	247 fewer per 1000 (from 6 fewer to 297 fewer)
Hypotension: children	60 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.14 (0 to 6.82)	33 per 1000	29 fewer per 1000 (from 33 fewer to 157 more)

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Valproate	Risk difference with Phenobarbital (95% CI)
Hypotension: adults	46 (2 studies)	LOW[1,2] due to risk of bias, imprecision	Peto OR 0.16 (0.32 to 0.82)	312 per 1000	245 fewer per 1000 (from 41 fewer to 186 fewer)
Transient depressed respiration: adults	133 (2 studies)	MODERATE[1,2] due to risk of bias	Peto OR 8.18 (1.78 to 37.71)	0 per 1000	100 more per 1000 (from 20 more to 190 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 21: Clinical evidence summary: Sodium valproate versus diazepam

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Diazepam	Risk difference with Valproate (95% CI)
Mortality: adults	65 (1 study)	LOW[1] due to imprecision	RR 2.92 (0.61 to 13.96)	57 per 1000	110 more per 1000 (from 22 fewer to 741 more)
Cessation of SE within 30 min: children	40 (1 study)	MODERATE[1] due to imprecision	RR 0.94 (0.71 to 1.25)	850 per 1000	51 fewer per 1000 (from 247 fewer to 213 more)
Cessation of SE within 1 hour: adults	66 (1 study)	LOW[1] due to imprecision	RR 0.9 (0.57 to 1.43)	556 per 1000	56 fewer per 1000 (from 239 fewer to 239 more)
Time for seizure cessation after drug administration (min): children	40 (1 study)	MODERATE[1] due to imprecision			The mean time for seizure cessation after drug administration (min) in the intervention groups was

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Diazepam	Risk difference with Valproate (95% CI)
					17.8 lower (29.94 to 5.66 lower)
Recurrence of seizure within 24 hours: children	35 (1 study)	LOW[1] due to imprecision	RR 0.8 (0.23 to 2.83)	250 per 1000	50 fewer per 1000 (from 192 fewer to 457 more)
ICU admission: children	40 (1 study)	MODERATE[1] due to imprecision	RR 0.58 (0.38 to 0.87)	950 per 1000	399 fewer per 1000 (from 123 fewer to 589 fewer)
Hypotension: children and adults	106 (2 studies)	HIGH	Peto OR 0.09 (0.02 to 0.3)	214 per 1000	220 fewer per 1000 (from 330 fewer to 120 fewer)
Respiratory depression: children	40 (1 study)	HIGH	Peto OR 0.06 (0.02 to 0.23)	600 per 1000	600 fewer per 1000 (from 820 fewer to 380 fewer)
Need for intubation: adults	66 (1 study)	LOW[1] due to imprecision	Peto OR 0.16 (0.01 to 2.57)	56 per 1000	60 fewer per 1000 (from 150 fewer to 40 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 22: Clinical evidence summary: Levetiracetam versus Fosphenytoin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fosphenytoin	Risk difference with Levetiracetam (95% CI)
Mortality	275 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW1,2	RR 1.94 (0.51	24 per 1000	23 more per 1000 (from 12 fewer to 153 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fosphenytoin	Risk difference with Levetiracetam (95% CI)
		due to risk of bias, imprecision	to 7.36)		
Cessation of SE from 10 - 20 minutes	116 (1 study)	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 0.98 (0.88 to 1.09)	931 per 1000	19 fewer per 1000 (from 112 fewer to 84 more)
Cessation of seizure within 5 minutes	50 (1 study)	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.10 (0.89 to 1.35)	840 per 1000	84 more per 1000 (from 92 fewer to 294 more)
Cessation of SE (and improvement in consciousness at 60 min without other anticonvulsant medications)	263 (1 study) 60 minutes	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.04 (0.8 to 1.36)	449 per 1000	18 more per 1000 (from 90 fewer to 162 more)
Time to seizure cessation	50 (1 study)	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean time to seizure cessation in the control groups was 2.5 minutes	The mean time to seizure cessation in the intervention groups was 0.80 higher (0.09 to 1.51 higher)
Seizure recurrence within 24 hours (within 60 mins to 12 hours after start of trial drug infusion)	325 (2 studies) 60 mins to 12 hours	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.07 (0.59 to 1.95)	113 per 1000	8 more per 1000 (from 46 fewer to 108 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fosphenytoin	Risk difference with Levetiracetam (95% CI)
Seizure recurrence within 48 hours	116 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.77 (0.37 to 1.61)	224 per 1000	52 fewer per 1000 (from 141 fewer to 137 more)
Length of hospital stay	50 (1 study)	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean length of hospital stay in the control groups was 5.8 days	The mean length of hospital stay in the intervention groups was 0.50 higher (1.91 lower to 2.91 higher)
Length of PICU stay	50 (1 study)	⨁⨁⨁⊖ MODERATE1 due to risk of bias		The mean length of PICU stay in the control groups was 42.3 hours	The mean length of PICU stay in the intervention groups was 1.70 higher (25.88 lower to 29.28 higher)
ICU admission	263 (1 study) 30 days	⨁⨁⨁⊖ MODERATE1 due to risk of bias	RR 1.01 (0.83 to 1.25)	593 per 1000	6 more per 1000 (from 101 fewer to 148 more)
Hypotension (defined as life threatening, within 60 mins after start of trial-drug infusion)	275 (1 study) 60 minutes	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.21 (0.02 to 1.84)	32 per 1000	25 fewer per 1000 (from 31 fewer to 27 more)
Respiratory depression	325 (2 studies)	⨁⨁⊖⊖ LOW1,2 due to risk of	RR 0.57 (0.29	120 per 1000	52 fewer per 1000 (from 85 fewer to 17 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fosphenytoin	Risk difference with Levetiracetam (95% CI)
		bias, imprecision	to 1.14)		
Bradycardia	116 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto 0.14 (0.00 to 6.82)	17 per 1000	15 fewer per 1000 (from 17 fewer to 100 more)
Tracheal Intubation	116 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.33 (0.04 to 3.11)	52 per 1000	35 fewer per 1000 (from 50 fewer to 109 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 23: Clinical evidence summary: Levetiracetam versus valproate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Valproate	Risk difference with Levetiracetam (95% CI)
Mortality	342 (2 studies) 30 days	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 1.94 (0.53 to 7.1)	19 per 1000	18 more per 1000 (from 9 fewer to 114 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Valproate	Risk difference with Levetiracetam (95% CI)
Cessation of SE within 15 minutes	67 (1 study)	⨁⨁⨁⨀ MODERATE3 due to imprecision	RR 1.13 (0.95 to 1.35)	829 per 1000	108 more per 1000 (from 41 fewer to 290 more)
Time to seizure cessation	67 (1 study)	⨁⨁⨁⨀ MODERATE3 due to imprecision		The mean time to seizure cessation in the control groups was 3.2 minutes	The mean time to seizure cessation in the intervention groups was 0.10 lower (0.75 lower to 0.55 higher)
Cessation of SE (and improvement in consciousness at 60 min without other anticonvulsant medications)	263 (1 study) 60 minutes	⨁⨁⨀⨀ LOW1,3 due to risk of bias, imprecision	RR 1.04 (0.8 to 1.36)	449 per 1000	18 more per 1000 (from 90 fewer to 162 more)
Seizure recurrence within 24 hours (within 60 mins to 12 hours after start of trial drug infusion)	275 (1 study) 60 mins to 12 hours	⨁⨀⨀⨀ VERY LOW1,3 due to risk of bias, imprecision	RR 0.95 (0.48 to 1.87)	112 per 1000	6 fewer per 1000 (from 58 fewer to 97 more)
Length of hospital stay	67 (1 study)	⨁⨁⨁⨀ MODERATE3 due to imprecision		The mean length of hospital stay in the control groups was 5.5 days	The mean length of hospital stay in the intervention groups was 1.50 higher (1.63 lower to 4.63 higher)
Length of PICU admission	67 (1 study)	⨁⨁⨁⨀ MODERATE3 due to imprecision		The mean length of PICU admission in the control groups was 10 days	The mean length of PICU admission in the intervention groups was 4.0 lower (5.97 to 2.03 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Valproate	Risk difference with Levetiracetam (95% CI)
ICU admission	266 (1 study)	⊕⊕⊕⊖ MODERATE1 due to risk of bias	RR 1.02 (0.84 to 1.25)	587 per 1000	12 more per 1000 (from 94 fewer to 147 more)
Hypotension (defined as life threatening, within 60 mins after start of trial-drug infusion)	275 (1 study) 60 minutes	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 0.42 (0.04 to 4.54)	16 per 1000	9 fewer per 1000 (from 15 fewer to 57 more)
Respiratory depression	275 (1 study)	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 1.00 (0.45 to 2.24)	80 per 1000	0 fewer per 1000 (from 44 fewer to 99 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 24: Clinical evidence summary: Fosphenytoin versus valproate

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Valproate	Risk difference with Fosphenytoin (95% CI)
Mortality: children and adults	250 (1 study)	VERY LOW[1] due to risk of bias, imprecision	RR 1.50 (0.26 to 8.82)	16 per 1000	8 more per 1000 (from 12 fewer to 125 more)

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Valproate	Risk difference with Fosphenytoin (95% CI)
Cessation of SE within 60 min: children and adults	239 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 0.97 (0.74 to 1.28)	463 per 1000	14 fewer per 1000 (from 120 fewer to 130 more)
Seizure recurrence within 24 hours: children and adults	250 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.00 (0.50 to 2.01)	112 per 1000	0 fewer per 1000 (from 56 fewer to 113 more)
ICU admission: children and adults	239 (1 study)	MODERATE[2] due to risk of bias	RR 1.01 (0.82 to 1.25)	587 per 1000	6 more per 1000 (from 106 fewer to 147 more)
Hypotension: children and adults	250 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 2.00 (0.37 to 10.72)	16 per 1000	16 more per 1000 (from 10 fewer to 156 more)
Respiratory depression: children and adults	250 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.60 (0.76 to 3.39)	80 per 1000	48 more per 1000 (from 19 fewer to 191 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

See Appendix F: section for full GRADE tables.

1.3.6 Economic evidence

1.3.6.1 Included studies

No health economic studies were included.

1.3.6.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G: Section G.2.

1.3.7 Economic model

This area was not prioritised for a new cost-effectiveness analysis.

1.3.8 Unit costs

Relevant unit costs are provided below to aid consideration of cost-effectiveness. The most commonly used drugs reported in the included clinical evidence are reported here for an illustration of unit costs.

Other resources may be required like an IV line and solution to dilute the drug for infusion.

Table 25: UK costs of drugs used as add on therapy for Status Epilepticus

Drug	Description	Cost	Dose	Cost per dose	Cost source
Sodium valproate					
Solution for injection	300mg/3ml 5 ampoules	£27.49	2.8g[(a)]	£54.98	eMIT
Phenytoin					
Solution for injection	250mg/5ml 5 ampoules	£3.37	1g	£2.69	eMIT
Leveritacetam					
Solution for injection	500mg/5ml 10 infusion vials	£28.37	2g – 4g	£11.35 - £22.69	eMIT
Diazepam					
Solution for injection	10mg/2ml 10 ampoules	£3.95	10mg[(b)]	£0.40	eMIT
Buccal midazolam					
Solution for injection	10mg/5ml 10 ampoules	£7.26	10mg[(b)]	£0.73	BNF
Phenobarbital					
Solution for injection	200mg/1ml 10 ampoules	£58.50	700mg	£23.40[(c)]	eMIT

Sources: Electronic Market Information Tool (eMIT), 09/01/20[45]. British National Formulary (BNF), 13/07/21[23]

(a) Based on the average dose reported in the ESET trial (40mg per kg) and assuming a person weighs on average 70kg[75]

(b) 10mg and then an additional 10mg if required. Cost is presented for 10mg

(c) Assuming the remainder of the medication cannot be used

All other sources of doses from the GC

1.3.9 Evidence statements

1.3.9.1 Effectiveness/Qualitative

- None.

1.3.9.2 Economic

- No relevant economic evaluations were identified.

1.4 The committee's discussion of the evidence

1.4.1 Interpreting the evidence

1.4.1.1 The outcomes that matter most

All outcomes included in these reviews were considered to be critical outcomes. These included time to seizure cessation, quality of life, and healthcare resource use. The following outcomes were considered harms; mortality, seizure recurrence, length of hospital stay, ICU admission, length of ICU stay and adverse events of respiratory depression, hypotension, frequency of endotracheal intubation, and neuropsychological events such as confusion, anxiety, challenging behaviour and mood disturbance. The status epilepticus reviews also included the critical outcomes of seizure recurrence within less than 24 hours of initial treatment (harm) and mean Glasgow Outcome Scale.

1.4.1.2 The quality of the evidence

<u>AED monotherapy for status epilepticus</u>

The quality of the evidence ranged from high to very low quality. Evidence was evenly distributed in either the moderate-, low- or very low categories. Studies were downgraded due to lack of allocation concealment or imprecision or both.

<u>AED add-on treatment for status epilepticus</u>

The quality of the evidence ranged from high to very low quality. Most of the evidence was of very low quality. Studies were downgraded due to lack of allocation concealment or imprecision or both.

<u>AED monotherapy for repeated or clusters of seizures</u>

Two studies were included with the quality of evidence consisting of moderate, low and very low quality for the three included outcomes. Studies were downgraded due to lack of allocation concealment or imprecision or both.

<u>AED add-on treatment for repeated or clusters of seizures</u>

Two studies were included with the quality of evidence being of either moderate or low quality. Studies were downgraded due to lack of allocation concealment or imprecision or both.

<u>AED monotherapy and add-on treatment for prolonged seizures</u>

No evidence was found for AED treatments for prolonged seizures

1.4.1.3 Benefits and harms

<u>AED monotherapy for status epilepticus</u>

The evidence was from 20 randomised controlled trials assessing convulsive status epilepticus (SE), with 2 studies including adults only and 2 studies including a mixed population of adults and children, and the remaining 16 trials included children only. The studies available evaluated diazepam, lorazepam, midazolam, levetiracetam, paraldehyde, phenobarbital, phenytoin and valproate. Evidence was found for the following comparisons (note some studies examined more than 1 comparison):

- diazepam versus placebo (1 study)
- diazepam versus lorazepam (3 studies)
- diazepam versus midazolam (10 studies)
- lorazepam versus placebo (1 study)
- lorazepam versus levetiracetam (1 study)
- lorazepam versus paraldehyde (1 study)
- lorazepam versus phenobarbital (1 study)
- lorazepam versus or phenytoin (1 study)
- valproate versus phenytoin (1 study)
- phenytoin versus phenobarbital (1 study)

The evidence showed a clinically important benefit for diazepam compared with placebo for termination of SE at time of arrival at ED, and a trend for an overall clinically important benefit for mortality, termination of seizures within 10 minutes and seizure recurrence within 24 hours. With the exception of mortality, no evidence was found for the other harm outcomes.

There was a trend for a clinically important benefit for diazepam compared with lorazepam for the termination of SE at time of arrival at ED. There was a clinically important benefit for diazepam compared with lorazepam for termination of SE within 5 minutes while in contrast there was a clinically important benefit for midazolam compared with diazepam for this outcome. There was a trend for a clinically important benefit for midazolam compared with diazepam for the outcome of termination of seizure within 10 minutes. Diazepam and lorazepam were clinically equivalent for this outcome. There was a clinically important benefit for diazepam compared with lorazepam for the outcome of termination of seizure within 20 minutes. Time to seizure cessation was equivalent for diazepam and lorazepam, as was time to cessation after drug administration for diazepam and midazolam. In terms of harms, there was no evidence of a clinically important difference for diazepam compared with lorazepam and midazolam for the outcome of mortality. There was a trend for a clinically important benefit of midazolam compared with diazepam for harm outcome of seizure recurrence within 24 hours, while lorazepam and diazepam were equivalent. There was a trend for a clinically important benefit for diazepam compared with midazolam for the adverse event of respiratory depression while no evidence of benefit for diazepam compared with lorazepam for respiratory depression. The only other harm was hypotension, and there was a trend for a clinically important benefit for diazepam compared with midazolam.

The evidence showed a clinically important benefit for lorazepam compared with placebo for termination of SE at time of arrival at ED, and a trend overall clinically important benefit for mortality.

There was no evidence of the benefit of lorazepam compared with diazepam and paraldehyde for termination of SE within 10 minutes. There was a clinically important benefit of lorazepam compared with diazepam for termination of SE at time of arrival at ED, while, conversely, there was clinical benefit for midazolam versus lorazepam for this outcome. Termination of SE within 30 minutes for lorazepam and levetiracetam was clinically equivalent as was time to seizure cessation for lorazepam compared with midazolam. For the outcomes of harms, there was no evidence of clinically important benefit for lorazepam for mortality compared with diazepam, levetiracetam or paraldehyde. There was no clinically

important benefit of lorazepam compared with diazepam, levetiracetam, midazolam or paraldehyde for the outcome of seizure recurrence within 24 hours. There was a trend for a clinically important benefit for midazolam compared with lorazepam for length of hospital stay, while in contrast there was trend for a clinical benefit for lorazepam compared with midazolam for the outcome of length of ICU stay. There was a trend for a clinical benefit of levetiracetam compared with lorazepam for the adverse events outcomes of respiratory failure and hypotension. Hypotension was equivalent for lorazepam compared with diazepam, midazolam, phenobarbital and phenytoin.

There was a clinically important benefit - for valproate for termination of SE after drug infusion compared with phenytoin. Seizure freedom at 24 hours was equivalent for the two drugs. There was a clinically important benefit for valproate compared with phenytoin for the harm outcome of seizure recurrence within 24 hours. There was a clinically important benefit for phenytoin versus phenobarbital for the adverse event of hypotension.

The committee considered there was no clear evidence to support one drug over another but agreed that valproate is not generally used historically in the UK as the first-line option. The evidence demonstrated that the benefit of all AEDs outweighed the harms. Although much of the evidence found was in children, it was thought appropriate to make recommendations for all populations as treatment decisions are considered similar for both adults and children. This was based on the experience and expertise of the committee.

The committee agreed to recommend benzodiazepines as first-line option for immediate use for SE, reflecting the evidence and current standard clinical practice. The committee acknowledged it was important to consider the setting when recommending which route of administration. Intravenous lorazepam is routinely given in hospitals, and it is rapid in action. The committee's experience was that lorazepam causes less respiratory depression and sedation relative to other drugs. The committee agreed that intravenous lorazepam should be given as first-line treatment option if intravenous access and resuscitation facilities were readily available.

The committee acknowledged intravenous access would not be readily available in the community. Buccal midazolam is more commonly used in community settings, and based on their experience and the evidence, the committee agreed that it should remain as the first choice, with rectal diazepam as an alternative if agreed based on previous use or if buccal midazolam is unavailable. The committee discussed that the rectal route of administration is the least preferred and not routinely chosen. The importance of having a tailored and individualised patient emergency care plan was discussed, and it was agreed that the administration of any drugs by trained community caregivers should be detailed within the patient's individual care plan.

The committee discussed how the speed of delivery could be more important than the benzodiazepine administered, as it is imperative a suitable drug is given as soon as possible to stop the seizure and aid recovery. If SE has not stopped within 5 minutes of administration of a first dose of benzodiazepine, a second dose would be given as standard practice.

The committee noted no evidence was found for non-convulsive seizures but suggested that a benzodiazepine would also be the first-line option for this population.

<u>AED add-on therapies for status epilepticus when first-line treatment has failed</u>

The evidence was from 21 randomised controlled trials assessing SE after failure on one AED, with 9 studies assessing adults, 11 assessing children and 1 assessing a mixture of adults and children. Participants had not responded to benzodiazepines. The comparisons included the following drugs when first-line therapy had failed:

- sodium valproate versus phenytoin (4 studies)
- sodium valproate versus phenobarbital (2 studies)

- levetiracetam versus phenytoin (7 studies)
- levetiracetam versus sodium valproate (1 study)
- lignocaine versus midazolam (1 study)
- sodium valproate versus lacosamide (1 study)
- midazolam versus diazepam (1 study)
- propofol versus midazolam (1 study)
- sodium valproate versus diazepam (2 studies)
- levetiracetam versus fosphenytoin (3 studies)

The majority of the studies evaluated AEDs administered intravenously.

There was a trend for a clinical benefit of sodium valproate compared with phenytoin for the outcomes of cessation of SE within 20 minutes, cessation of SE within 12 hours and cessation of SE within 7 days. Evidence for harms showed a trend for clinical benefit of sodium valproate for seizure recurrence within 24 hours. There was clinical benefit for valproate compared with phenytoin for the adverse events of respiratory depression and hypotension.

There was a trend for a clinical benefit of levetiracetam compared with phenytoin for the outcomes of cessation of seizure within 5 minutes, cessation of seizure within 30 minutes and cessation of SE within 24 hours. There was no evidence of benefit of levetiracetam compared with phenytoin for cessation of SE within 2 hours. Mean duration of SE in good responders was equivalent for the two drugs, as was good outcome at discharge according to the Functional Independence Measure (FIM). Phenytoin showed a trend for a clinical benefit for good outcome at discharge according to the mRS score. In terms of harms, there was a trend for a clinical benefit of levetiracetam compared with phenytoin for the outcome of mortality. There was a trend for a clinical benefit of levetiracetam versus phenytoin for recurrence of seizures within 24 hours. The evidence showed equivalence for the harm outcome of hypertension. - Phenytoin showed a trend for a clinically important difference for the harms of length of hospital stay, admission to critical care and confusion compared with levetiracetam.

Lignocaine showed clinically important benefit compared with midazolam for the outcomes of cessation of SE, length of ICU stays and intubation needing mechanical intubation.

There was a trend for a clinical benefit of valproate compared with lacosamide for the outcome of time for seizure cessation after drug administration and seizure freedom within 24 hours. There was clinical equivalence for cessation of SE for 1 hour. Considering harms, there was a trend for a clinical benefit of lacosamide compared with valproate for the outcome of mortality, while for hypotension, clinical equivalence was found.

There was a trend for a clinically importance benefit of diazepam compared with midazolam for the outcomes of, time to final seizure and seizure recurrence whilst on infusion. Diazepam and midazolam showed clinical equivalence for time to initial seizure cessation, cessation of SE within 6 hours. In terms of harms there was a trend for a clinically importance benefit of diazepam compared with midazolam and a clinically important difference for seizure recurrence after stopping infusion. Diazepam and midazolam showed clinical equivalence for hypotension.

There was a trend for a clinically important benefit of midazolam compared with propofol for the harm outcomes of mortality and hypotension. There was a trend for an evidence of benefit of propofol compared with midazolam for cessation of SE for 48 hours.

Phenobarbital showed a trend for a clinically important benefit compared with valproate for the harm outcomes of mortality and for hypotension. Valproate showed trend for a clinically important benefit compared with phenobarbital for seizure cessation within 20 minutes and

clinically important benefit for the harm outcome of transient depressed respiration. In children, there was a clinically important benefit of valproate compared with phenobarbital for recurrence of seizure within 24 hours, while in adults, the converse was true.

Valproate and diazepam showed clinical equivalence for the outcome of cessation of SE within 30 minutes and 1 hour. there was clinical equivalence for the two drugs. There was a clinically important benefit of valproate compared with diazepam for time for seizure cessation after drug administration.

With respect to harms, diazepam showed a trend for a clinically important benefit compared with valproate for the outcome of mortality. Evidence showed that valproate had a clinically important benefit for ICU admission, hypotension and respiratory depression compared with diazepam. There was a trend for a benefit of valproate for seizure recurrence within 24 hours and need for intubation.

Evidence found that there was clinical equivalence for fosphenytoin and levetiracetam for the outcomes of cessation of SE within 5, 10 to 20, and 60 minutes. There was a trend for benefit of fosphenytoin for time to seizure cessation. Considering harms, fosphenytoin showed a trend for a clinically important benefit compared with levetiracetam for the outcome of mortality, while for seizure recurrence 24 hours and seizure recurrence within 48 hours there was clinical equivalence. There was clinical equivalence for fosphenytoin and levetiracetam for the following harm outcomes; ICU admission, length of hospital stay, length of PICU stay. There was a trend for evidence of benefit for levetiracetam compared with fosphenytoin for respiratory depression, hypotension. Clinical equivalence was found for bradycardia and the need for intubation.

There was clinical equivalence for valproate and levetiracetam drugs for the outcomes of cessation of SE within 60 minutes and seizure cessation within 24 hours. There was clinical equivalence for valproate compared with levetiracetam for the harm outcome of mortality. Evidence showed clinical equivalence for the other harmful outcomes of ICU admission, depression and hypotension.

Evidence showed clinical equivalence for valproate and fosphenytoin for the outcomes of cessation of SE within 60 minutes and seizure cessation within 24 hours and ICU admission. In terms of harms, valproate showed a trend for a clinically important benefit compared with fosphenytoin for the outcomes of mortality, respiratory depression and hypotension.

The committee agreed there was no evidence to support the selection of one of these drugs over another because of the overall clinical equivalence demonstrated in the studies. Therefore, any would be appropriate unless specific conditions mandated a restriction of choice (for example, previous allergic reaction to phenytoin). The committee, therefore, agreed to recommend one of levetiracetam, phenytoin or valproate as first-line add-on treatment. The committee discussed the importance of the choice being individualised and patient centred.

There were also two studies on general anaesthetics, with lignocaine and propofol, as well as phenobarbital showing clinical benefit for the outcomes of mortality, cessation of SE, seizure recurrence within 24 hours (adults), length of ICU stay, intubation need and the adverse event of hypotension. The committee decided to recommend the use of general anaesthetics or phenobarbital as third-line treatment options if the first- and second-line treatments were ineffective.

The committee discussed the importance of being aware of the different circumstances that could also cause SE, such as pregnancy, hypoglycaemia, alcohol withdrawal or autoimmune epilepsy where additional treatments may be required. The need to differentiate psychogenic non-epileptic seizures from seeming convulsive SE was also discussed.

The committee noted that there were two particularly significant trials included in the review. It was discussed how the ESETT trial showed results for fosfenytoin, levetiracetam and

valproate that were overall equivalent and noted that this was a well conducted trial. The ECLIPSE trial showed phenytoin to be beneficial. The committee noted that these trials might encourage levetiracetam use owing to the ease of transitioning to longer term therapy with levetiracetam, perhaps particularly in women of child-bearing potential as levetiracetam has relatively low teratogenic potential. The GC noted that all the studies within this review were conducted in a hospital setting.

AED monotherapy and add-on therapies for repeated seizures and clusters of seizures

For monotherapy of repeated seizures or clusters of seizures, two small trials in adults and children comparing diazepam with placebo were included. A clinically important benefit was shown for diazepam for seizure freedom and patients requiring additional emergency treatment. A clinically important benefit for placebo was shown for harm outcomes of the nervous system including abnormal coordination, dizziness, euphoria, nervousness and somnolence.

For add-on therapy two comparisons were included, comparing levetiracetam with phenytoin and midazolam with diazepam. A clinically important benefit was shown for levetiracetam and diazepam overall.

The committee agreed that due to a lack of evidence, a research recommendation should be made. They noted that the definition of repeated/cluster seizures varies. Acute repetitive or cluster seizures are a medical emergency. The committee noted clobazam and midazolam often used in practice and made a consensus recommendation for their use.

AED Monotherapy and add-on therapies for prolonged seizures

No studies were found for prolonged seizures and the committee made consensus recommendations.

The committee defined prolonged seizures as seizures lasting more than 2 minutes above the typical duration of a person's seizure, but less than 5 minutes. The committee noted that midazolam is often used and discussed that once an individualised patient care plan is in place, then this is a reasonable route to take. The committee noted that following a first episode of prolonged seizures in a person with a known diagnosis of epilepsy the person should be seen by a specialist. It is possible for further prolonged seizures to be managed in the community once a midazolam protocol is in place. This protocol will need to be regularly reviewed by an epilepsy nurse.

No evidence was found for non-convulsive status epilepticus. The committee was unable to make general recommendations although the committee noted that benzodiazepines would usually be the first treatment of choice. The committee also noted that it was important not to over-sedate people in non-convulsive SE. This was because the risk of injury and mortality from non-convulsive SE is generally less than from convulsive SE. The committee noted that excessive sedation of patients could, for example, result in unnecessary intubation and other co-morbidities. The committee noted that people with non-convulsive epilepsy should have individualised and specialist advice. The committee agreed further research is needed and developed a research recommendation for this population.

1.4.1.4 Cost effectiveness and resource use

AED monotherapy for status epilepticus

Two economic evaluations were included for the status epilepticus monotherapy question. Both were from a UK NHS perspective (Lee 2013 was from Wales, and Lee 2014 was from Scotland), and decision analyses looking at the branded version of buccal midazolam (buccolam) compared to standard practice (as defined by clinicians), buccal midazolam (non Buccolam product) and rectal diazepam.

Lee 2013 defined standard practice for Wales as 95% buccal midazolam, and 5% rectal diazepam. The population was paediatric patients with a diagnosis of epilepsy suffering prolonged, acute, convulsive seizures in the community setting. The time horizon was 6 years. This was a probabilistic discrete event simulation and decision tree model based on a single UK RCT (McIntyre 2005). The discrete event simulation part of the model simulated 5000 patients for each treatment. For each of these patients, the frequency, location of seizures, and the initial store of drugs at each location were simulated at the start of the model. The availability of medication at each location was then adjusted by the occurrence of seizures within the model time horizon. If the model reached a point where drugs were disposed of due to expiry, then the value of the disposed products were calculated, and new products ordered. The decision tree part of the model calculated the likelihood of events once a seizure occurred, like whether medication was available, and if treatment was administered by parent/caregiver, and the probability of going to hospital. As the model was produced as a submission for a health technology appraisal for the approval of Buccolam, then the model is structured in a way that captures the benefit of the branded product, such as the fact that it comes packaged with 4 pre-filled syringes that can be split between locations. The study showed that Buccolam dominated all comparators. This was rated as partially applicable, because it was a UK study, but the EQ-5D was filled in by clinicians rather than patients or their parents/carers, which conflicts with the NICE reference case. The study was rated as having potentially serious limitations because the costs were out of date, as in the BNF there is only one product of buccal Midazolam that is not Buccolam. This is called Epistatus, and based on current BNF costs would be more expensive now because it only comes in one pre-filled syringe. However, costs depend on the dose and how it is packaged (separate pre-filled multiple syringes or not) so there is uncertainty about how the result of the study might be affected, as there are also generic versions of buccal midazolam available which are not listed in the BNF. There is also a conflict of interest because it is funded by the manufacturers of Buccolam, and most inputs were assumptions elicited from surveys of clinicians or parents.

Lee 2014 has the same structure as Lee 2013, and used the same trial for effectiveness data, but is from a Scottish perspective; therefore, some of the inputs are different because they were elicited from clinicians specific to Scotland. Standard care in this study was 100% buccal midazolam. The study had a 1-year time horizon. This also found that Buccolam dominated all comparators and was also rated as partially applicable with potentially serious limitations.

Buccal administrations tend to be more expensive than rectal or IV. However, as mentioned above, there is some uncertainty about prices and what can be acquired locally compared to the nationally available information.

The committee's interpretation of the clinical evidence for this question, was that benzodiazepines are effective for the treatment of status epilepticus in a community setting, and it is difficult to distinguish within the class or between administration types. The committee drafted recommendations that they felt were in line with current practice, where buccal midazolam is used in the community. If IV access is available, then lorazepam was recommended as this is commonly used in a hospital setting for the treatment of status epilepticus.

<u>AED add-on treatment for status epilepticus</u>

No economic evidence was identified.

The clinical review showed that a variety of drugs had clinical benefit, such as sodium valproate, levetiracetam, and phenytoin. One of the studies included showed clinical equivalence between fosphenytoin, levetiracetam and valproate. While fosphenytoin was used in the trial, in the UK phenytoin is more commonly administered for SE. There are differences in costs between the different drugs, with sodium valproate and levetiracetam being more expensive. The committee decided to recommend that either levetiracetam,

phenytoin or sodium valproate, as adjunctive treatments if seizures have continued after administration of benzodiazepines. Although some drugs might have higher costs, the committee explained that clinicians can prefer different drugs in different circumstances, for example, because, phenytoin requires cardiac monitoring during administration and because valproate should be avoided in people with underlying mitochondrial disorders'.

Recommendations were also made for third-line treatment based on committee consensus of current practice.

AED monotherapy and add-on therapies for repeated seizures and clusters of seizures

No economic evidence was identified for these questions. The committee made consensus recommendations and decided to make a research recommendation but noted that clobazam is typically used for repeated clusters and seizures.

The recommendations made are reflective of current practice and so are not expected result in a significant resource impact.

AED Monotherapy and add-on therapies for prolonged seizures

No economic evidence was identified for these questions. The committee wanted to make clear in a recommendation what the definition of a prolonged seizure is and how it should be treated immediately.

The committee agreed that all the recommendations made are likely to be in line with current practice.

1.4.1.5 Other factors the committee took into account

The committee discussed how the operational definitions of status epilepticus (SE) had changed recently. While it was previously held that a seizure had to persist for thirty minutes to be classified as SE, the International League Against Epilepsy (ILAE) have proposed a new definition of SE. According to the consensus statement (Trinka et al., 2015), two relevant time points are proposed. t1 is considered the point at which mechanisms to prevent abnormally prolonged seizures become ineffective. t2 is the point beyond which status epilepticus can cause, for example, loss or injury to nerve cells and changes to nerve cell networks.

This conceptual definition allows for t1 (after which seizure activity is thought continuous) and t2 (after which there is a risk of long-term consequences) to be different for different seizure types. For bilateral tonic clonic seizures, t1 is 5 minutes and t2 30 minutes.

The committee, therefore, defined SE for the purposes of all searches as seizures lasting 5 minutes or more. This was chosen to include more recent literature and also because setting a short time threshold would capture more papers.

AED add-on treatment for status epilepticus

The committee also acknowledged that in current clinical practice levetiracetam is more routinely used compared to phenytoin and valproate, mainly due to the ease of administration and efficacy.

However, the evidence has shown that they are all equally effective. Side effect profiles of each of the medications need to be taken into consideration and tailored for the person. This is particularly important for Phenytoin considering the risk of teratogenicity in women of childbearing age. It is also important to note that this advice is for use in emergency administration. Long term treatment needs to be discussed with the person and their emergency care plan should be updated to include what medications worked for them to control their seizures (in the emergency setting). The committee highlighted that people who have had status epilepticus seizures and their families or carers are given safety advice to

follow, such as precautions around bathing, swimming and night-time supervision and would always be closely followed up in a seizure clinic over the next 6 – 12 months.

1.5 Recommendations supported by this evidence review

This evidence review supports recommendations 7.1.1 to 7.1.12 in the NICE guideline.

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Appendices

Appendix A: Review protocols

A.1 Review protocol: monotherapy for status epilepticus

ID	Field	Content
0.	PROSPERO registration number	CRD42019155853
1.	Review title	What antiepileptic drugs (monotherapy) are effective in the treatment of status epilepticus?
2.	Review question	What antiepileptic drugs (monotherapy) are effective in the treatment of status epilepticus?
3.	Objective	The aim of the review is to identify which are the most effective drugs in the treatment of status epilepticus as first line treatment. Recommendations will cover the most appropriate treatments.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Generalised convulsive and non-convulsive status epilepticus are neurological and medical emergencies defined as 5 or more minutes of either continuous seizure activity or repetitive seizures with no intervening recovery of consciousness. Convulsive status epilepticus presents as overt convulsive activity (tonic and/or clonic) making them easy to diagnose clinically. Non-convulsive status epilepticus is status epilepticus without obvious tonic–clonic activity
6.	Population	Inclusion: Children, young people and adults with status epilepticus (convulsive and non-convulsive) Strata: Convulsive status epilepticus Non-convulsive status epilepticus (focal, myoclonic, absence) Exclusion: New-born babies (under 28 days) with acute symptomatic seizures
7.	Intervention/Exposure/Test	Brivaracetam Carbamazepine (for focal motor status) Chlormethiazole (clomethiazole) Clobazam Clonazepam (for myoclonic status) Chloral hydrate Diazepam Eslicarbazepine Fosphenytoin Gabapentin General anaesthetic induction agents Immunotherapy

		Intravenous immunoglobulin Lacosamide Levetiracetam Lorazepam Midazolam Oxcarbazepine Paraldehyde Perampanel Phenobarbital (phenobarbitone) Phenytoin Pregabalin Rufinamide Steroids (methylprednisolone, prednisolone) Stiripentol Topiramate Valproate (sodium valproate / valproic acid) Zonisamide Dose according to prescriber discretion and / or local protocols
8.	Comparator/Reference standard/Confounding factors	• One drug vs placebo / no treatment • One drug vs another drug
9.	Types of study to be included	• RCTs • Systematic reviews of RCTs Exclusion: Non-English publications, non-randomised studies, conference abstracts It is anticipated that there will be sufficient RCT evidence that there is no need to search for non-randomised studies.
10.	Other exclusion criteria	Non-English language studies.

		Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Status epilepticus, a state of prolonged, uncontrolled seizures, is a common emergency department presentation that is potentially life-threatening. Untreated, the mortality approaches 30%, whilst following evidence based, validated treatment can significantly improve outcomes.
12.	Primary outcomes (critical outcomes)	• mortality (including SUDEP) • time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, up 24 hours for convulsive and non-convulsive- up to 1 month • time to event seizure cessation • seizure recurrence < within less than 24 hours after administration of monotherapy • time to seizure recurrence after administration of monotherapy • quality of life (QOLIE-31, QOLIE-AD-48) • length of ICU stay • length of hospital stay • mean Glasgow outcome scale (% difference in the means between the two groups) • adverse events – respiratory depression – hypotension – frequency of endotracheal intubation – ICU admission – neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance • healthcare resource use
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two

		reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. For intervention reviews EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Systematic reviews will be assessed by Risk of Bias in Systematic Reviews (ROBIS) randomised controlled trials by Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.
17.	Analysis of sub-groups	Statistically heterogeneity will be assessed by visually examining the forest plots and by calculating the I^2 inconsistency statistic (with an I^2 value of more than 50% indicating considerable heterogeneity.

		• according to the risk of bias of individual studies • by age (children vs adults) • study location (UK, US, Europe, rest of the world) • drug dose • route of administration • non-convulsive status epilepticus by type: focal vs myoclonic vs absence)	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date		
22.	Anticipated completion date		
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☐
		Piloting of the study selection process	☐ / ☐
		Formal screening of search results against eligibility criteria	☐ / ☐
		Data extraction	☐ / ☐

		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact: Angela Cooper National Guideline Centre angela.cooper@rcplondon.ac.uk 5b Named contact e-mail epilepsies@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Gill Ritchie, Guideline Lead Angela Cooper, Senior Research Fellow Rafina Yarde, Systematic reviewer Margaret Constanti, Senior Health economist Joseph Runicles, Information specialist		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE		

		guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112 .	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Status epilepticus, antiepileptic drugs	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

A.2 Review protocol: add-on therapy for status epilepticus

ID	Field	Content

0.	PROSPERO registration number	CRD42019155854
1.	Review title	What antiepileptic drugs (add-on therapy) are effective in the treatment of status epilepticus?
2.	Review question	What antiepileptic drugs (add-on therapy) are effective in the treatment of status epilepticus?
3.	Objective	The aim of the review is to identify which are the most effective drugs in the treatment of status epilepticus when first line therapy has failed. Recommendations will cover the most appropriate treatments.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Add-on therapy is required for people who do not respond to initial treatment for status epilepticus. Status epilepticus can be convulsive or non-convulsive in nature. Generalised convulsive and non-convulsive status epilepticus are neurological and medical emergencies defined as 5 or more min of either continuous seizure activity or repetitive seizures with no intervening recovery of consciousness.

		Convulsive status epilepticus presents as overt convulsive activity (tonic and/or clonic) making them easy to diagnose clinically. Non-convulsive status epilepticus is status epilepticus without obvious tonic–clonic activity
6.	Population	Inclusion: Children, young people and adults with status epilepticus (convulsive and non-convulsive) who are non-responsive to first line therapy. Strata: Convulsive status epilepticus Non-convulsive status epilepticus (focal vs myoclonic vs absence) Exclusion: New-born babies (under 28 days) with acute symptomatic seizures
7.	Intervention/Exposure/Test	Brivaracetam Carbamazepine (for focal motor status) Chlormethiazole (clomethiazole) Clobazam Clonazepam (for myoclonic status) Chloral hydrate Diazepam Eslicarbazepine Fosphenytoin General anaesthetic induction agents Immunotherapy Intravenous immunoglobulin Lacosamide Levetiracetam Lorazepam Midazolam Oxcarbazepine

		Oxygen Paraldehyde Perampanel Phenobarbital (phenobarbitone) Phenytoin Rufinamide Stiripentol Steroids (methylprednisolone, prednisolone) Topiramate Valproate (sodium valproate / valproic acid) Zonisamide Dose according to prescriber discretion and / or local protocols
8.	Comparator/Reference standard/Confounding factors	• One add-on drug vs monotherapy • One add-on drug vs different add-on drug • Add-on drug vs failure on initial therapeutic management (for example 2 drugs previously administered)
9.	Types of study to be included	• RCTs • Systematic reviews of RCTs Exclusion: Non-English publications, non-randomised studies, conference abstracts It is anticipated that there will be sufficient RCT evidence that there is no need to search for non-randomised studies.
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Status epilepticus, a state of prolonged, uncontrolled seizures, is a common emergency department presentation that is potentially life-threatening. Untreated, the mortality approaches 30%, whilst following evidence based, validated treatment can significantly improve outcomes. The

		seizure may resolve after treatment with one drug, although sometimes additional treatment is required.

12.	Primary outcomes (critical outcomes)	• mortality (including SUDEP)
		• time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive))
		• time to event seizure cessation
		• seizure recurrence greater than or less than 24 hours after administration of monotherapy
		• time to seizure recurrence after administration of monotherapy
		• quality of life (QOLIE-31, QOLIE-AD-48)
		• length of ICU stay
		• length of hospital stay
		• mean Glasgow outcome scale (% difference in the means between the two groups)
		• adverse events
		  ○ respiratory depression
		  ○ hypotension
		  ○ frequency of endotracheal intubation
		  ○ ICU admission
		  ○ Neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance
		• healthcare resource use

13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. For intervention reviews EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Systematic reviews will be assessed by Risk of Bias in Systematic Reviews (ROBIS) randomised controlled trials by Cochrane RoB (2.0)

		10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.	
17.	Analysis of sub-groups	Statistically heterogeneity will be assessed by visually examining the forest plots and by calculating the I^2 inconsistency statistic (with an I^2 value of more than 50% indicating considerable heterogeneity. • according to the risk of bias of individual studies • by age (children vs adults) • study location (UK, US, Europe, rest of the world) • drug dose • route of administration • non-convulsive status epilepticus by type: focal vs myoclonic vs absence	
18.	Type and method of review	☒	Intervention

		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	Oct 2019	
22.	Anticipated completion date	Jan 2020	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☑
		Piloting of the study selection process	☐ / ☑
		Formal screening of search results against eligibility criteria	☐ / ☑
		Data extraction	☐ / ☑
		Risk of bias (quality) assessment	☐ / ☑
		Data analysis	☐ / ☑
24.	Named contact	5a. Named contact: Angela Cooper National Guideline Centre	

		angela.cooper@rcplondon.ac.uk 5b Named contact e-mail epilepsies@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Gill Ritchie, Guideline Lead Angela Cooper, Senior Research Fellow Rafina Yarde, Systematic reviewer Margaret Constanti, Senior Health economist Joseph Runicles, Information specialist
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the min of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112 .
29.	Other registration details	
30.	Reference/URL for published protocol	

31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Status epilepticus, antiepileptic drugs	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

A.3 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2004 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[135] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with "Minor limitations" then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with "Very serious limitations", then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:*

	• UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

This literature search strategy was used for the following reviews:

- What AEDs (monotherapy) are effective in the treatment of repeated seizures or clusters of seizures?
- What AEDs (add-on therapy) are effective in the treatment of repeated seizures or clusters of seizures?
- What antiepileptic drugs (monotherapy) are effective in the treatment of status epilepticus?
- What antiepileptic drugs (add-on therapy) are effective in the treatment of status epilepticus?
- What AEDs (monotherapy) are effective in the treatment of prolonged seizures?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[135]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 26: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 May 2021	Randomised controlled trials Systematic review studies Exclusions
Embase (OVID)	1974 – 13 May 2021	Randomised controlled trials Systematic review studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 5 of 12 CENTRAL to 2021 Issue 5 of 12	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/

8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	exp Anticonvulsants/
28.	exp Acetazolamide/
29.	exp Carbamazepine/
30.	exp Chloral hydrate/
31.	exp Clomethiazole/
32.	exp Clonazepam/
33.	exp Clorazepate Dipotassium/
34.	exp Diazepam/
35.	exp Ethosuximide/
36.	exp Levetiracetam/
37.	exp Lorazepam/
38.	exp Mephenytoin/
39.	exp Mephobarbital/
40.	exp Midazolam/
41.	exp Methazolamide/
42.	exp Nitrazepam/
43.	exp Paraldehyde/
44.	exp Pentobarbital/
45.	exp Phenobarbital/
46.	exp Phenytoin/
47.	exp Primidone/
48.	exp Propofol/
49.	exp Temazepam/
50.	exp Thiopental/
51.	exp Topiramate/
52.	exp Trimethadione/
53.	exp Valproic Acid/
54.	exp Vigabatrin/

55.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline).ti,ab.
56.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*).ti,ab.
57.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide).ti,ab.
58.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide).ti,ab.
59.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate).ti,ab.
60.	hyperbaric oxygen.ti,ab.
61.	(Hydrocortisone or prednisolone or dexamethasone or methylprednisolone or corticosteroids).ti,ab.
62.	*Adrenal Cortex Hormones/ or *adrenocorticotropic hormone/ or *cosyntropin/
63.	(Adrenocorticotropic hormone or adrenocorticotropin or corticotropin or cosyntropin or tetracosactrin).ti,ab.
64.	or/27-63
65.	randomized controlled trial.pt.
66.	controlled clinical trial.pt.
67.	randomi#ed.ti,ab.
68.	placebo.ab.
69.	randomly.ti,ab.
70.	Clinical Trials as topic.sh.
71.	trial.ti.
72.	or/65-71
73.	Meta-Analysis/
74.	exp Meta-Analysis as Topic/

75.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
76.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
77.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
78.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
79.	(search* adj4 literature).ab.
80.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
81.	cochrane.jw.
82.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
83.	or/73-82
84.	26 and 64
85.	84 and (72 or 83)

1 **Embase (Ovid) search terms**

1.	exp epilepsy/
2.	seizure/
3.	epileptic state/
4.	febrile convulsion/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	exp Anticonvulsants/
26.	exp Acetazolamide/
27.	exp Carbamazepine/
28.	exp Chloral hydrate/
29.	exp Clomethiazole/
30.	exp Clonazepam/
31.	exp Clorazepate Dipotassium/

32.	exp Diazepam/
33.	exp Ethosuximide/
34.	exp Lorazepam/
35.	exp Mephenytoin/
36.	exp Mephobarbital/
37.	exp Midazolam/
38.	exp Methazolamide/
39.	exp Nitrazepam/
40.	exp Paraldehyde/
41.	exp Pentobarbital/
42.	exp Phenobarbital/
43.	exp Phenytoin/
44.	exp Primidone/
45.	exp Propofol/
46.	exp Temazepam/
47.	exp Thiopental/
48.	exp Topiramate/
49.	exp Trimethadione/
50.	exp Valproic Acid/
51.	exp Vigabatrin/
52.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline).ti,ab.
53.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*).ti,ab.
54.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide).ti,ab.
55.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide).ti,ab.

56.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate).ti,ab.
57.	hyperbaric oxygen.ti,ab.
58.	(Hydrocortisone or prednisolone or dexamethasone or methylprednisolone or corticosteroids).ti,ab.
59.	(Adrenocorticotropic hormone or adrenocorticotropin or corticotropin or cosyntropin or tetracosactrin).ti,ab.
60.	*corticosteroid/ or *tetracosactide/
61.	or/25-60
62.	random*.ti,ab.
63.	factorial*.ti,ab.
64.	(crossover* or cross over*).ti,ab.
65.	((doubl* or singl*) adj blind*).ti,ab.
66.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
67.	crossover procedure/
68.	single blind procedure/
69.	randomized controlled trial/
70.	double blind procedure/
71.	or/62-70
72.	systematic review/
73.	meta-analysis/
74.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
75.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
76.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
77.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
78.	(search* adj4 literature).ab.
79.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
80.	cochrane.jw.
81.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
82.	or/72-81
83.	24 and 61
84.	83 and (71 or 82)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Epilepsy] explode all trees
#2.	MeSH descriptor: [Seizures] explode all trees
#3.	MeSH descriptor: [Status Epilepticus] explode all trees
#4.	MeSH descriptor: [Seizures, Febrile] explode all trees
#5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Anticonvulsants] explode all trees
#8.	MeSH descriptor: [Acetazolamide] explode all trees

#9.	MeSH descriptor: [Carbamazepine] explode all trees
#10.	MeSH descriptor: [Chloral Hydrate] explode all trees
#11.	MeSH descriptor: [Chlormethiazole] explode all trees
#12.	MeSH descriptor: [Clonazepam] explode all trees
#13.	MeSH descriptor: [Clorazepate Dipotassium] explode all trees
#14.	MeSH descriptor: [Diazepam] explode all trees
#15.	MeSH descriptor: [Ethosuximide] explode all trees
#16.	MeSH descriptor: [Lorazepam] explode all trees
#17.	MeSH descriptor: [Mephenytoin] explode all trees
#18.	MeSH descriptor: [Mephobarbital] explode all trees
#19.	MeSH descriptor: [Midazolam] explode all trees
#20.	MeSH descriptor: [Methazolamide] explode all trees
#21.	MeSH descriptor: [Nitrazepam] explode all trees
#22.	MeSH descriptor: [Paraldehyde] explode all trees
#23.	MeSH descriptor: [Pentobarbital] explode all trees
#24.	MeSH descriptor: [Phenobarbital] explode all trees
#25.	MeSH descriptor: [Phenytoin] explode all trees
#26.	MeSH descriptor: [Primidone] explode all trees
#27.	MeSH descriptor: [Propofol] explode all trees
#28.	MeSH descriptor: [Temazepam] explode all trees
#29.	MeSH descriptor: [Thiopental] explode all trees
#30.	MeSH descriptor: [Topiramate] explode all trees
#31.	MeSH descriptor: [Trimethadione] explode all trees
#32.	MeSH descriptor: [Valproic Acid] explode all trees
#33.	MeSH descriptor: [Vigabatrin] explode all trees
#34.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline):ti,ab
#35.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*):ti,ab
#36.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide):ti,ab
#37.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or

	temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide):ti,ab
#38.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate):ti,ab
#39.	hyperbaric oxygen:ti,ab
#40.	(Hydrocortisone or prednisolone or dexamethasone or methylprednisolone or corticosteroids):ti,ab
#41.	(Adrenocorticotropic hormone or adrenocorticotropin or corticotropin or cosyntropin or tetracosactrin):ti,ab
#42.	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#43.	MeSH descriptor: [Adrenocorticotropic Hormone] explode all trees
#44.	MeSH descriptor: [Cosyntropin] explode all trees
#45.	(or #7-#44)
#46.	#6 and #45

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to an Epilepsies population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 27: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1946 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Embase	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1974 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 May 2021 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/

5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.

49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

1 **Embase (Ovid) search terms**

1.	exp *epilepsy/
2.	*landau kleffner syndrome/
3.	exp *seizure/
4.	"seizure, epilepsy and convulsion"/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/

29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	sickness impact profile/
41.	(quality adj2 (wellbeing or well being)).ti,ab.
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
55.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58.	or/39-57
59.	24 and (38 or 58)

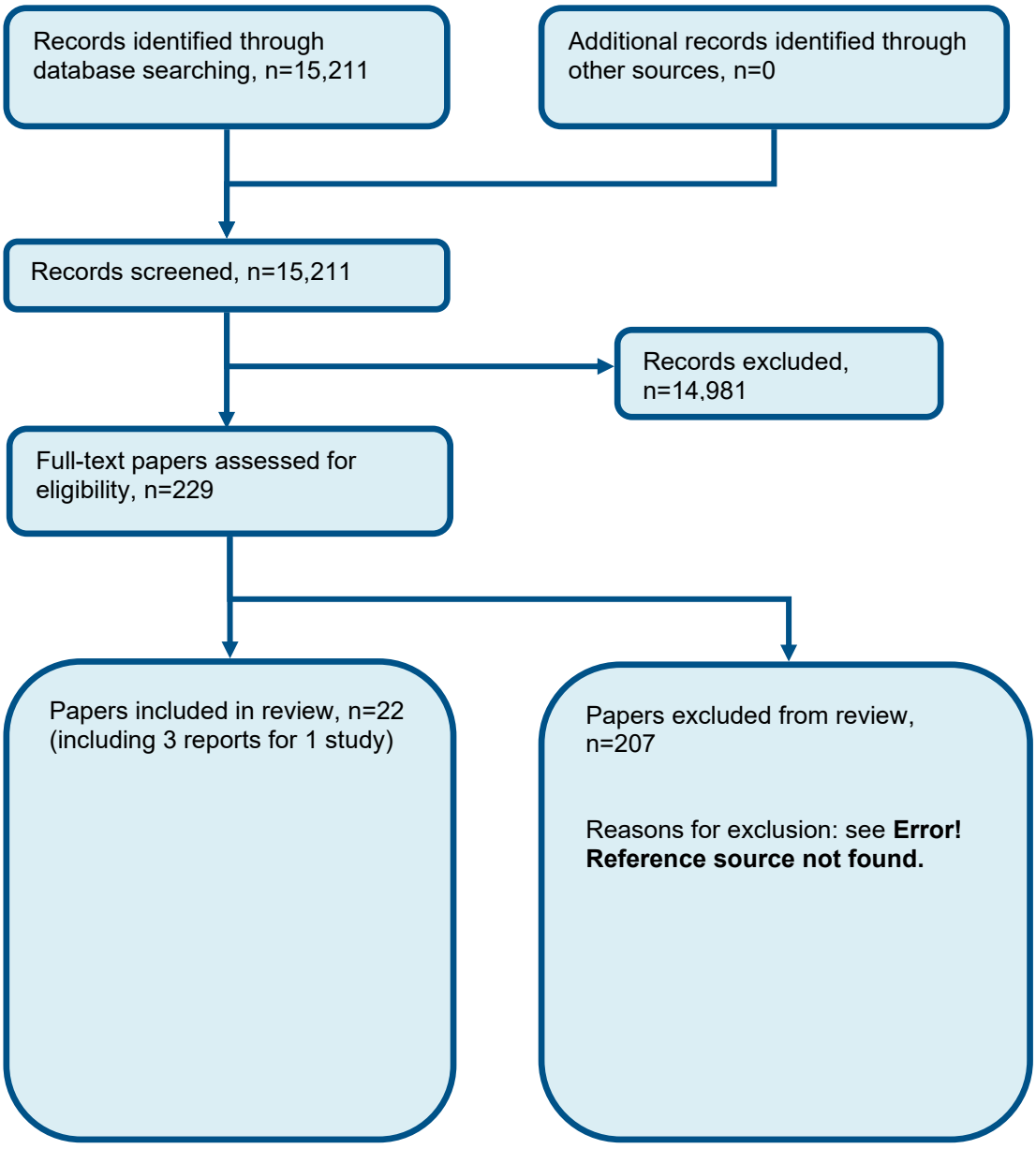
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Seizures EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Status Epilepticus EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Seizures, Febrile EXPLODE ALL TREES
#5.	((dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome))
#6.	#1 OR #2 OR #3 OR #4 OR #5

Appendix C: Clinical evidence selection

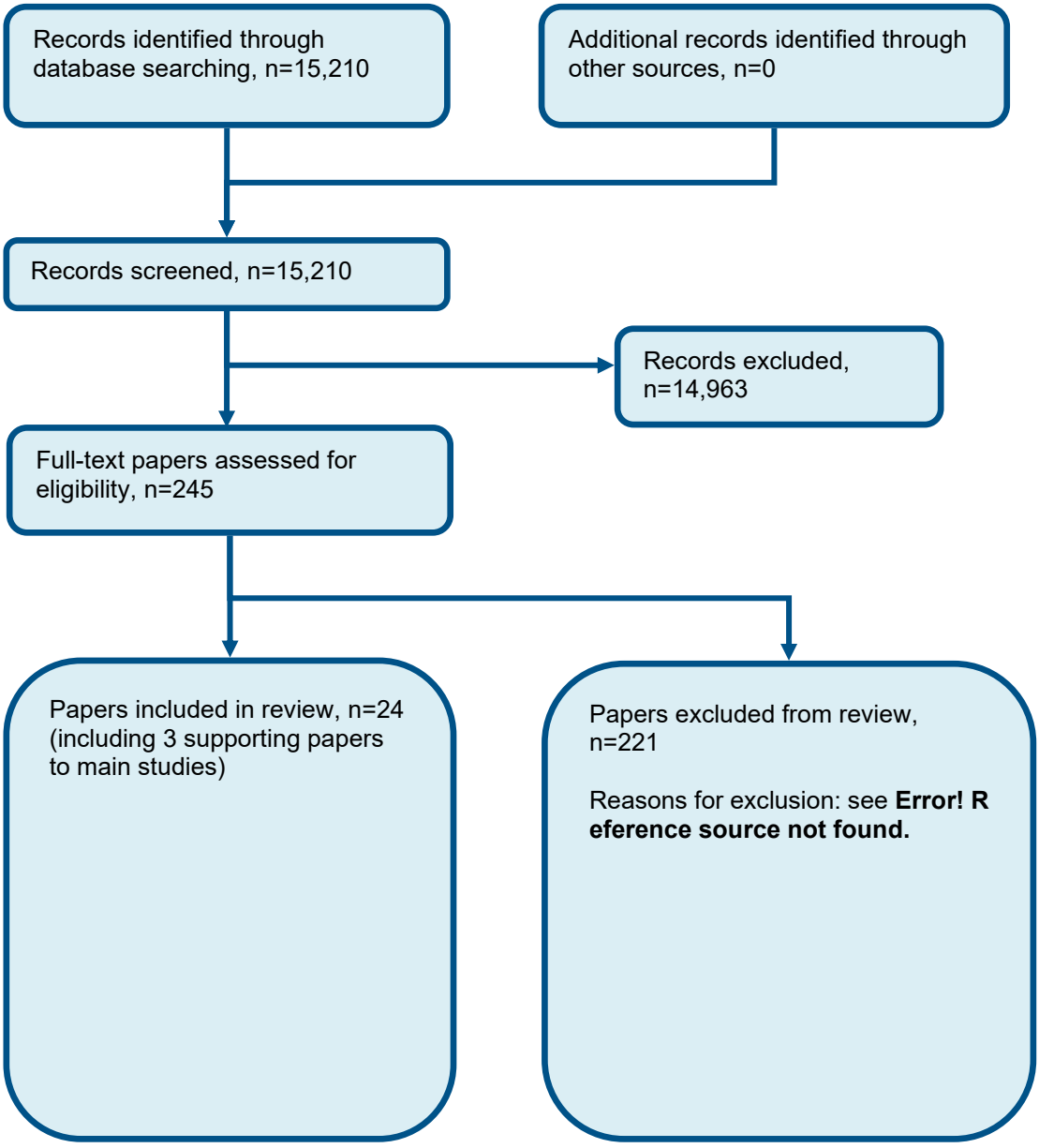
C.1 Monotherapy

Figure 1: Flow chart of clinical study selection for the review of monotherapy for status epilepticus



C.2 Add on Therapies

Figure 2: Flow chart of clinical study selection for the review of add-on therapy for status epilepticus



Appendix D: Clinical evidence tables

D.1 Monotherapy

Study	**Ahmad 2006[5]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in Malawi; Setting: ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Convulsions greater than 5 min
Stratum	Convulsive status epilepticus: Convulsive
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 2 months to 12 years presenting with acute generalized convulsions for a minimum of 5 min
Exclusion criteria	Any child who received anticonvulsant agent within an hour of presentation, whose seizures stopped with cooling or hypoglycaemia correction, or features consistent with hepatic or hypertensive encephalopathy, or organophosphate poisoning
Recruitment/selection of patients	Consecutive

Age, gender and ethnicity	Age - Median (IQR): Lorazepam: 18.5 (9-33) months, Paraldehyde: 19 (10.5-36) months. Gender (M:F): 55%/45%. Ethnicity: Not stated
Further population details	1. Age: Children 2. Non convulsive by type: N/A
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Drug - Paraldehyde. Intramuscular paraldehyde (0.2ml/kg) was drawn into a syringe and delivered immediately into the buttock or thigh after sterilisation of the injection site. Duration Start of seizure to end of seizure. Concurrent medication/care: Humidified oxygen. Indirectness: No indirectness Further details: 1. Dose: Define (0.2 ml/kg). 2. Risk of bias of studies: Low risk of bias 3. Route of administration: intramuscular 4. Study location: Rest of the world (n=80) Intervention 2: Drug - Lorazepam. Intranasal 100 micrograms/kg - was drawn up in a ml syringe, attached to a mucosal atomization device and squirted rapidly into a nostril. Duration Seizure start to end. Concurrent medication/care: Humidified oxygen. Indirectness: No indirectness Further details: 1. Dose: Define (100 micrograms/kg). 2. Risk of bias of studies: Low risk of bias 3. Route of administration: oral (intranasal). 4. Study location: Rest of the world
Funding	Academic or government funding (College of Emergency Medicine (UK))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LORAZEPAM versus PARALDEHYDE

Protocol outcome 1: Mortality (including SUDEP) at study endpoint
- Actual outcome: Mortality at study endpoint; Group 1: 15/80, Group 2: 13/80
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Cause of seizures lorazepam/paraldehyde; Cerebral malaria - 49%/55%, febrile - 20%/19%, metabolic derangement - 15%/15%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint - Actual outcome: Seizure stopped within 10 min at 10 min; Group 1: 60/80, Group 2: 49/80 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Cause of seizures lorazepam/paraldehyde; Cerebral malaria - 49%/55%, febrile - 20%/19%, metabolic derangement - 15%/15%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 3: Time to event seizure cessation at study endpoint - Actual outcome: Time to seizure cessation (min) at N/A; Lorazepam - 7.5 min (4.5 to 11.5) Paraldehyde - 8 (5 to 21); Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 4: Time to seizure recurrence after administration of monotherapy at study endpoint - Actual outcome: Seizure recurrence within 24 hours at 24 hours; Group 1: 8/80, Group 2: 11/80 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Cause of seizures lorazepam/paraldehyde; Cerebral malaria - 49%/55%, febrile - 20%/19%, metabolic derangement - 15%/15%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Seizure recurrence within less than 24 hours after administration of monotherapy at 24 hours; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint; Healthcare resource use at study endpoint

Study	**Alldredge 2001[7]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=205)
Countries and setting	Conducted in USA; Setting: Treatment out-of-hospital before arrival at ED
Line of therapy	1st line
Duration of study	Intervention + follow up: Arrival at hospital
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults (18 years of age or older) with an out-of-hospital diagnosis of status epilepticus, status epilepticus was defined as continuous or repeated seizure activity for more than five min without recovery of consciousness
Exclusion criteria	Pregnancy, if intravenous access could not be established, or if transported by a private ambulance company or were in police custody, pulse of less than 60 beats per min, a systolic blood pressure of less than 100 mm Hg, second- or third-degree atrioventricular block, sustained ventricular tachyarrhythmia, asthma or chronic obstructive pulmonary disease, a history of long-term use of benzodiazepines, or sensitivity to benzodiazepines.

Age, gender and ethnicity	Age Mean (SD): lorazepam: 49.9 (20.1), diazepam: 50.4 (19.1), placebo: 52.0 (18.2) Male gender (%): lorazepam: 69.7, diazepam: 60.3, placebo: 59.1. Ethnicity: Lorazepam vs diazepam vs placebo- White 49% vs 54% vs 47%, Black 18% vs 16% vs 29%, Asian or pacific islander 21% vs 7% vs 10%
Further population details	1. Age: adults 2. Non convulsive by type: N/A
Indirectness of population	No indirectness
Interventions	(n=71) Intervention 1: Placebo. Placebo. Duration Time before arrival at hospital. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Dose: Not applicable 2. Risk of bias of studies: Low risk of bias 3. Route of administration: Not applicable 4. Study location: US
Funding	Academic or government funding (National Institute for Health (US))
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint; Time to event seizure cessation at study endpoint; Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint; Healthcare resource use at study endpoint

Study	**Appleton 1995[10]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=61)
Countries and setting	Conducted in United Kingdom; Setting: ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Seizure
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Children presenting with convulsions
Exclusion criteria	Non detailed
Age, gender and ethnicity	Age - Other: Mean age (years) - Intravenous diazepam 5.2, rectal diazepam 3.8, intravenous lorazepam 6.6, rectal lorazepam 3.3. Gender (M:F): Male: female - Intravenous diazepam 2:1, rectal diazepam 1:1, intravenous lorazepam 2:1, rectal lorazepam 3:1. Ethnicity: Not stated
Further population details	1. Age: Children 2. Non convulsive by type: N/A
Indirectness of population	No indirectness

Interventions	(n=34) Intervention 1: Drug - Diazepam. Intravenous and rectal 0.3 to 0.4 mg/kg. Duration Intravenously administered over 15 to 30 seconds. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Dose: Define (0.3 to 0.4 mg/kg). 2. Risk of bias of studies: High risk of bias 3. Route of administration: intravenous (Intravenous and rectal). 4. Study location: UK (n=27) Intervention 2: Drug - Lorazepam. Intravenous and rectal 0.05 to 0.1 mg/kg. Duration Intravenously administered over 15 to 30 seconds. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Dose: Define (Intravenous and rectal 0.05 to 0.1 mg/kg). 2. Risk of bias of studies: High risk of bias 3. Route of administration: intravenous (Intravenous and rectal). 4. Study location: UK
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAZEPAM versus LORAZEPAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome for Convulsive status epilepticus : Time to seizure cessation (seconds) at 20-60 seconds (range); Mean; mean (range): diazepam seizure cessation = 26 (20-51) seconds, lorazepam seizure cessation = 29 (25 to 60) seconds;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Diazepam vs Lorazepam: known epilepsy - 60% vs 67%, neurological disorder - 21% vs 24%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Time to event seizure cessation at study endpoint
- Actual outcome for Convulsive status epilepticus : Seizure recurrence at 24 hours; Group 1: 12/34, Group 2: 6/27
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Diazepam vs Lorazepam: known epilepsy - 60% vs 67%, neurological disorder - 21% vs 24%; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Convulsive status epilepticus : Cessation of seizure after first dose with 7 to 8 min at 7 to 8 min; Group 1: 22/34, Group 2: 19/27
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Diazepam vs Lorazepam: known epilepsy - 60% vs 67%, neurological disorder - 21% vs

24%; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint; Healthcare resource use at study endpoint

Study	**Ashrafi 2010[13]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=98)
Countries and setting	Conducted in Iran; Setting: ED
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 hour
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Prolonged convulsive seizures lasting more than 5 min and those convulsing while attending the ED
Exclusion criteria	Not stated
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age – Median: Midazolam 24 months, diazepam 48 months. Gender (M:F): 58/40. Ethnicity: Not stated
Further population details	1. Age: Children 2. Non convulsive by type.
Indirectness of population	No indirectness

Interventions	(n=49) Intervention 1: Drug - Midazolam. Buccal midazolam: 0.3 to 0.5 mg/kg Duration Not stated. Concurrent medication/care: Non stated Further details: 1. Dose: Define (0.3 to 0.5 mg/kg). 2. Risk of bias of studies: Low risk of bias 3. Route of administration: oral 4. Study location: Rest of the world (n=49) Intervention 2: Drug - Diazepam. Rectal diazepam: 0.5 mg/kg Duration Not stated. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Dose: (Rectal diazepam: 0.5 mg/kg). 2. Risk of bias of studies: Low risk of bias 3. Route of administration: rectal 4. Study location: Rest of the world
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus DIAZEPAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome for Convulsive status epilepticus : Seizure cessation at 5 min; Group 1: 49/49, Group 2: 40/49
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Midazolam vs diazepam: generalised tonic-clonic seizures-
86% vs 86%, myoclonic seizures- 14% vs 10% Group 1 Number missing N/A: ; Group 2 Number missing: N/A

Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to event seizure cessation at study endpoint; Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as

	confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint; Healthcare resource use at study endpoint

Study	**Chamberlain 1997[38]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=25)
Countries and setting	Conducted in USA; Setting: ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 60 min follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Children between the ages of birth and 18 years and presenting to the ED with motor seizures of at least 10 min duration were eligible for participation.
Exclusion criteria	Patients excluded if they already had an IV line established or had received anticonvulsants for the current seizure episode.
Age, gender and ethnicity	Age - Median (range): midazolam - 42 months (9-165), diazepam - 39 (3-112). Gender (M:F): 17 male, 7 female. Ethnicity: Not stated
Further population details	1. Age: Children 2. Non convulsive by type.
Indirectness of population	No indirectness

Interventions	(n=13) Intervention 1: Drug - Midazolam. Midazolam - IV midazolam 0.2 mg/kg (maximum 7 mg). Duration N/A. Concurrent medication/care: If the patients seizure stopped within five min after administration of medication, then the treatment was considered successful. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: USA (n=11) Intervention 2: Drug - Diazepam. Diazepam - IV diazepam 0.3mg/kg (maximum 10 mg). Duration N/A. Concurrent medication/care: If the patients seizure stopped within five min after administration of medication, then the treatment was considered successful. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus DIAZEPAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome: Time to cessation after medication at N/A; Group 1: mean 4.5 (SD 3); n=13, Group 2: mean 3.4 (SD 2); n=11
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: generalised tonic-clonic; midazolam - 10, diazepam - 5; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Protocol deviation

Protocol outcome 2: Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours
- Actual outcome: Recurrent seizures at <24 hours; Group 1: 4/13, Group 2: 4/11
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: generalised tonic-clonic; midazolam - 10, diazepam - 5; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Protocol deviation

Protocol outcome 3: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint
- Actual outcome: Respiratory depression at N/A; Group 1: 0/13, Group 2: 0/11

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: generalised tonic-clonic; midazolam - 10, diazepam - 5; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Protocol deviation	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to event seizure cessation at study endpoint; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Chamberlain 2014[41]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=310)
Countries and setting	Conducted in USA; Setting: ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 3 months to younger than 18 years were eligible for inclusion if they exhibited generalized tonic-clonic status epilepticus. Status epilepticus was defined as either(1) 3 or more convulsions within the preceding hour and currently experiencing a convulsion; (2) 2 or more convulsions in succession with no recovery of consciousness and currently experiencing a convulsion; or (3) a current single convulsion of at least 5min' duration. Seizures may have started focally and then generalized; however, to be included, the patients had to have loss of consciousness and generalized tonic-clonic seizures. These definitions are consistent with current standards for therapy.
Exclusion criteria	Patients were excluded if they met any of the following criteria prior to medication administration: known pregnancy; hypotension; significant cardiac dysrhythmia; need for emergent surgical intervention and general anaesthesia; known contraindication to benzodiazepine use; or benzodiazepine use within the preceding 7 days, including use of anticonvulsant medications by ambulance personnel. Patients were

	terminated from the study (early terminators) if the investigators discovered 1 of the exclusionary criteria after receiving study medication or if the family refused participation in the study.
Age, gender and ethnicity	Age - Mean (SD): diazepam - 4.9 years (4.9), lorazepam - 4.8 years (4.6). Gender (M:F): 155 male, 155 female. Ethnicity: Black - 111, White - 149, Asian - 7, American Indian - 2, Native Hawaiian - 3, more than one race - 18, other - 14, Not reported - 6
Further population details	1. Age: Children 2. Non convulsive by type: N/A
Indirectness of population	No indirectness
Interventions	(n=162) Intervention 1: Drug - Diazepam. IV Diazepam - based on estimated patient weight to deliver a final dose of 0.2 mg/kg of diazepam (maximum dose, 8 mg). The medication was handed to the treating team, who administered it by slow intravenous (IV) push for 1 min. The end of the IV push was defined as time 0. Duration N/A. Concurrent medication/care: Opaque syringe cylinders were used to prevent visualizing the medication. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=148) Intervention 2: Drug - Lorazepam. IV Lorazepam - based on estimated patient weight to deliver a final dose of 0.1 mg/kg of lorazepam (maximum dose, 4 mg). Duration N/A. Concurrent medication/care: Opaque syringe cylinders were used to prevent visualizing the medication. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Academic or government funding (This study was funded by grant HHSN275201100017C from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The Paediatric Emergency Care Applied Research Network (PECARN) is supported by cooperative agreements U03MC00001,U03MC00003,U03MC00006, U03MC00007, andU03MC00008 from the Emergency Medical Services for Children (EMSC) program of the Maternal and Child Health Bureau (MCHB), Health Resources and Services Administration, Department of Health and Human Services. The Best Pharmaceuticals for Children Act Data Coordinating Center for this study was the EMMESCorp and was funded by the NICHD under a separate contract.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAZEPAM versus LORAZEPAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome: Cessation of status epilepticus within 10 min of initial dose of medication and a sustained absence of convulsions for 30 min at 10 min; Group 1: 101/140, Group 2: 97/133
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Seizure aetiology by group diazepam/lorazepam; febrile - 35%/30.1%, low levels of anti-epileptic drugs - 8.6%/9.8%, acute symptomatic - 16.4%/11.3%; Group 1 Number missing: 22, Reason: 18 didn't have status epilepticus, 4 were duplicate participants ; Group 2 Number missing: 15, Reason: 13 didn't have status epilepticus, 3 were duplicate participants

Protocol outcome 2: Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours
- Actual outcome: Seizure recurrence within 1 hour at 1 hour; Group 1: 11/101, Group 2: 10/97
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Seizure aetiology by group diazepam/lorazepam; febrile - 35%/30.1%, low levels of anti-epileptic drugs - 8.6%/9.8%, acute symptomatic - 16.4%/11.3%; Group 1 Number missing: 22, Reason: 18 didn't have status epilepticus, 4 were duplicate participants ; Group 2 Number missing: 15, Reason: 13 didn't have status epilepticus, 3 were duplicate participants
- Actual outcome: Seizure recurrence within 4 hours at 4 hours; Group 1: 39/101, Group 2: 38/97
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Seizure aetiology by group diazepam/lorazepam; febrile - 35%/30.1%, low levels of anti-epileptic drugs - 8.6%/9.8%, acute symptomatic - 16.4%/11.3%; Group 1 Number missing: 22, Reason: 18 didn't have status epilepticus, 4 were duplicate participants ; Group 2 Number missing: 15, Reason: 13 didn't have status epilepticus, 3 were duplicate participants

Protocol outcome 3: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint
- Actual outcome: Respiratory depression at N/A; Group 1: 74/162, Group 2: 54/148
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Seizure aetiology by group diazepam/lorazepam; febrile - 35%/30.1%, low levels of anti-epileptic drugs - 8.6%/9.8%, acute symptomatic - 16.4%/11.3%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to event seizure cessation at study endpoint; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Fisgin 2002[57]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=45)
Countries and setting	Conducted in Turkey; Setting: ED
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 hour
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Seizure of at least 5 min
Exclusion criteria	None stated
Age, gender and ethnicity	Age - Mean (SD): Diazepam 2.02, Midazolam 3.8 years. Gender (M:F): Diazepam 11/11, Midazolam 8/15. Ethnicity: None stated
Further population details	1. Age: Children 2. Non convulsive by type: N/A
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Drug - Diazepam. Rectal diazepam: 0.3 mg/kg. Rectal diazepam: 0.3 mg/kg Duration Immediately. Concurrent medication/care: None stated

	Indirectness: No indirectness Further details: 1. Dose: Define (0.3 mg/kg). 2. Risk of bias of studies: High risk of bias 3. Route of administration: rectal 4. Study location: Rest of the world (n=23) Intervention 2: Drug - Midazolam. Intranasal midazolam: 0.2 mg/kg over 30 sec. Duration 30 sec. Concurrent medication/care: None stated. Indirectness: No indirectness Further details: 1. Dose: Define (0.2 mg/kg over 30 sec). 2. Risk of bias of studies: High risk of bias 3. Route of administration: oral (Intranasal). 4. Study location: Rest of the world
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAZEPAM versus MIDAZOLAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome for Convulsive status epilepticus : Seizure cessation at 10 min at 10 min; Group 1: 13/22, Group 2: 20/23
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Diazepam vs midazolam: febrile seizures- 23% vs 22%, non-febrile seizures 77% vs 78%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to event seizure cessation at study endpoint; Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint; Healthcare resource use at study endpoint

Study	**Gathwala 2012[59]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in India; Setting: ED
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Status epilepticus
Exclusion criteria	Systemic disease like liver or kidney disease, cardiovascular disorders, metabolic disorders such as diabetes mellitus, intravenous access could not be established
Age, gender and ethnicity	Age - Mean (SD): Diazepam: 6.19 (3.63) midazolam: 4.82 (2.48), lorazepam: 5.28 (2.97). Gender (M:F): 78/42. Ethnicity:
Further population details	1. Age: Children 2. Non convulsive by type: N/A
Indirectness of population	No indirectness

Interventions	(n=40) Intervention 1: Drug - Diazepam. 0.3 mg/kg diluted in 3 to 5 cc normal, dose infused over 2 min at 2mg/min, maximum dose was 5 mg in children > 5 years old and 10 mg in children 5 years or older if seizure persisted a repeat dose was given after an interval of 5 to 10 min. Duration 10 min. Concurrent medication/care: None stated. Indirectness: No indirectness Further details: 1. Dose: Define (0.3 mg/kg). 2. Risk of bias of studies: Low risk of bias 3. Route of administration: intravenous 4. Study location: Rest of the world (n=40) Intervention 2: Drug - Lorazepam. Intravenous lorazepam: 0.1 mg/kg diluted in 3 to 5 cc normal saline, dose infused over 1 to 2 min at 1 to 2 mg/min, maximum dose was 4 mg per dose and if seizure persisted, one more dose was given after an interval of 5 to 10 min. Duration 10 min. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Dose: Define (0.1 mg/kg). 2. Risk of bias of studies: Low risk of bias 3. Route of administration: intravenous 4. Study location: Rest of the world (n=40) Intervention 3: Drug - Midazolam. Intravenous midazolam: 0.1 mg/kg diluted in 3 to 5 cc normal saline, dose infused over 1 to 2 min at 1 to 2 mg/min, maximum dose was 5 mg per dose and if seizure persisted, one more dose was given after an interval of 5 to 10 min. Duration 10 min. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Dose: Define (0.1 mg/kg). 2. Risk of bias of studies: Low risk of bias 3. Route of administration: intravenous 4. Study location: Rest of the world
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAZEPAM versus LORAZEPAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint

- Actual outcome for Convulsive status epilepticus : Time to seizure cessation (sec) at Time to seizure cessation (sec); Group 1: mean 84.94 seconds (SD 38.56); n=40, Group 2: mean 91.12 seconds (SD 23.58); n=40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Lorazepam
Seizure disorder: 83%
Meningitis/encephalitis: 15%
Neurocysticercosis: 2%

Diazepam
Seizure disorder: 88%
Meningitis/encephalitis: 10%
Neurocysticercosis: 2%
Midazolam
Seizure disorder: 85%
Meningitis/encephalitis: 13%
Neurocysticercosis: 2%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint
- Actual outcome for Convulsive status epilepticus : Respiratory depression at Not stated; Group 1: 1/40, Group 2: 0/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Lorazepam
Seizure disorder: 83%
Meningitis/encephalitis: 15%
Neurocysticercosis: 2%

Diazepam
Seizure disorder: 88%
Meningitis/encephalitis: 10%
Neurocysticercosis: 2%
Midazolam
Seizure disorder: 85%
Meningitis/encephalitis: 13%

Neurocysticercosis: 2%; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAZEPAM versus MIDAZOLAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome for Convulsive status epilepticus : Time to seizure cessation (sec) at Time to seizure cessation; Group 1: mean 84.94 seconds (SD 38.56); n=40, Group 2: mean 92.69 seconds (SD 25.97); n=40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Lorazepam
Seizure disorder: 83%
Meningitis/encephalitis: 15%
Neurocysticercosis: 2%

Diazepam
Seizure disorder: 88%
Meningitis/encephalitis: 10%
Neurocysticercosis: 2%
Midazolam
Seizure disorder: 85%
Meningitis/encephalitis: 13%
Neurocysticercosis: 2%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint
- Actual outcome for Convulsive status epilepticus : Respiratory depression at Not stated; Group 1: 1/40, Group 2: 0/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Lorazepam
Seizure disorder: 83%
Meningitis/encephalitis: 15%
Neurocysticercosis: 2%

Diazepam

Seizure disorder: 88%
Meningitis/encephalitis: 10%
Neurocysticercosis: 2%
Midazolam
Seizure disorder: 85%
Meningitis/encephalitis: 13%
Neurocysticercosis: 2%; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LORAZEPAM versus MIDAZOLAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome for Convulsive status epilepticus : Time to seizure cessation (sec) at Time to seizure cessation (sec); Group 1: mean 91.12 seconds (SD 23.58); n=40, Group 2: mean 92.69 seconds (SD 25.97); n=40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Lorazepam
Seizure disorder: 83%
Meningitis/encephalitis: 15%
Neurocysticercosis: 2%

Diazepam
Seizure disorder: 88%
Meningitis/encephalitis: 10%
Neurocysticercosis: 2%
Midazolam
Seizure disorder: 85%
Meningitis/encephalitis: 13%
Neurocysticercosis: 2%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint
- Actual outcome for Convulsive status epilepticus : Respiratory depression at Not stated; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness ; Baseline details: Lorazepam Seizure disorder: 83% Meningitis/encephalitis: 15% Neurocysticercosis: 2% Diazepam Seizure disorder: 88% Meningitis/encephalitis: 10% Neurocysticercosis: 2% Midazolam Seizure disorder: 85% Meningitis/encephalitis: 13% Neurocysticercosis: 2%; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to event seizure cessation at study endpoint; Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Lahat 2000[87]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=44)
Countries and setting	Conducted in Israel; Setting: Paediatric ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All children between the ages of six months and five years who presented with febrile seizures (tonic, clonic, or tonic-clonic) lasting for at least 10 min were eligible for inclusion in our study. Febrile seizures were diagnosed retrospectively on the basis of clinical data (history, physical findings, and cerebrospinal fluid results).
Exclusion criteria	We excluded children with established intravenous lines or those who had received anticonvulsants before admission.
Age, gender and ethnicity	Age - Median (range): midazolam - 16 months (6-38), diazepam - 18 months (6-40). Gender (M:F): 25 male, 19 female. Ethnicity: Not stated.
Further population details	1. Age: 2. Non convulsive by type: N/A

Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Drug - Midazolam. Intranasal Midazolam - 0.2 mg/kg. Midazolam solution (5 mg/ml) was dripped by syringe into both nostrils in equal doses, and an intravenous line was immediately introduced. Treatment was considered successful if the seizure ceased within five min. Seizures that stopped between five and 10 min after treatment were defined as successful but delayed control of seizure. Duration N/A. Concurrent medication/care: During seizure activity and for 60 min after control, the children were followed by continuous cardiorespiratory and pulse oximetry monitors. Vital signs were recorded every 15 min. During seizure activity, high flow oxygen was provided through a mask. All the children were admitted to the paediatric ward for 24-hour observation after cessation of seizures. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=23) Intervention 2: Drug - Diazepam. Intravenous Diazepam - 0.3 mg/kg, the maximum dose being 10 mg. Duration N/A. Concurrent medication/care: During seizure activity and for 60 min after control, the children were followed by continuous cardiorespiratory and pulse oximetry monitors. Vital signs were recorded every 15 min. During seizure activity, high flow oxygen was provided through a mask. All the children were admitted to the paediatric ward for 24 hours observation after cessation of seizures. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus DIAZEPAM

Protocol outcome 1: Time to event seizure cessation at study endpoint
- Actual outcome: Time of cessation of seizure after drug administration. at N/A; Group 1: mean 3.1 (SD 2.2); n=21, Group 2: mean 2.5 (SD 1.9); n=23
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: cause of febrile seizures, midazolam/diazepam ; Upper respiratory tract infection - 10/10, Acute otitis media - 6/4, Bronchopneumonia - 3/4, Clinical dysentery (shigellosis) - 3/5, Others - 4/3; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours - Actual outcome: Treatment failure at N/A; Group 1: 3/21, Group 2: 2/23; Comments: Seizures that did not stop within 10 min after treatment were defined as treatment failures Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: cause of febrile seizures, midazolam/diazepam; Upper respiratory tract infection - 10/10, Acute otitis media - 6/4, Bronchopneumonia - 3/4, Clinical dysentery (shigellosis) - 3/5, Others - 4/3; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome: Seizure recurrence at N/A; Group 1: 1/21, Group 2: 1/23 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: cause of febrile seizures, midazolam/diazepam; Upper respiratory tract infection - 10/10, Acute otitis media - 6/4, Bronchopneumonia - 3/4, Clinical dysentery (shigellosis) - 3/5, Others - 4/3; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 3: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint - Actual outcome: Adverse events at N/A; Group 1: 0/21, Group 2: 0/23 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: cause of febrile seizures, midazolam/diazepam; Upper respiratory tract infection - 10/10, Acute otitis media - 6/4, Bronchopneumonia - 3/4, Clinical dysentery (shigellosis) - 3/5, Others - 4/3; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Mahmoudian 2004[110]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=70)
Countries and setting	Conducted in Iran; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention time: 10 min
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Randomly assigned 70 patients between 2 months and 15 years of age admitted to the emergency department of Alzahra Hospital in Isfahan with acute seizures.
Exclusion criteria	Children who had received anticonvulsants before admission were excluded.
Age, gender and ethnicity	Age - Range: 2 months to 15 years. Gender (M:F): not available. Ethnicity: Not stated
Further population details	1. Age: Children 2. Non convulsive by type: N/A
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Drug - Diazepam. Intravenous diazepam - 0.2mg/kg was administered to patients with odd numbers after an intravenous line was introduced. Duration N/A. Concurrent medication/care: During

	seizure activity, high flow oxygen by mask and routine life support were provided. All children admitted to the paediatric ward for evaluation of the aetiology of seizures. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=35) Intervention 2: Drug - Midazolam. Intranasal Midazolam - solution (5mg/ml) was dropped by syringe into both nostrils in equal doses to those with even numbers and an intravenous line was immediately introduced. Duration N/A. Concurrent medication/care: During seizure activity, high flow oxygen by mask and routine life support were provided. All children admitted to the paediatric ward for evaluation of the aetiology of seizures. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus DIAZEPAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome: Seizure control within 10 min at 10 min; Group 1: 35/35, Group 2: 35/35
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: aetiology of seizures, midazolam/diazepam; Hypocalcaemia - 2/8, Hypoglycaemia - 0/2, febrile convulsions - 14/1, epilepsy - 14/13, head trauma - 0/1, CNS infection - 4/10, hyponatremia - 1/0; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A
- Actual outcome: Mean interval between drug administration and seizure control at N/A; Group 1: mean 3.58 (SD 1.68); n=35, Group 2: mean 2.94 (SD 2.62); n=35
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: aetiology of seizures, midazolam/diazepam; Hypocalcaemia - 2/8, Hypoglycaemia - 0/2, febrile convulsions - 14/1, epilepsy - 14/13, head trauma - 0/1, CNS infection - 4/10, hyponatremia - 1/0; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint

- Actual outcome: Adverse events at N/A; Group 1: 0/35, Group 2: 0/35 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: aetiology of seizures, midazolam/diazepam; Hypocalcaemia - 2/8, Hypoglycaemia - 0/2, febrile convulsions - 14/1, epilepsy - 14/13, head trauma - 0/1, CNS infection - 4/10, hyponatremia - 1/0; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to event seizure cessation at study endpoint; Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Malu 2014[112]**
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=436)
Countries and setting	Conducted in Democratic Republic of the Congo, Rwanda; Setting: Hospitals
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients included in our study were children aged from 5months to 10 years admitted for seizures lasting more than 5 min between January 1, 2011, and August 15, 2012. Seizures were clinically categorized on the basis of the commonly used characteristics of seizures, that is, distribution, duration, and level of consciousness impairment. A diagnosis of status epilepticus was considered when seizures lasted for more than 30 min or repeated two times or more without any recovery. Those who recovered a normal level of consciousness between two seizures were classified as having serial seizures.
Exclusion criteria	Early expulsion of the medication within 10 min after administration was an exclusion criterion.
Age, gender and ethnicity	Age - Median (IQR): diazepam - 35.5 months (17.75 - 54), lorazepam - 35.5 months (19-60). Gender (M:F): 221 male, 215 female. Ethnicity: Not stated.

Further population details	1. Age: Children 2. Non convulsive by type: N/A
Indirectness of population	No indirectness
Interventions	(n=202) Intervention 1: Drug - Diazepam. Rectal diazepam - was administered at a dose of 0.5 mg/kg of body weight of a 1mg/mL reconstituted solution (Figure 1). Body weight was estimated by using the child's age. Thus, 2.5 mg of diazepam was given to children between 5 and 11 months old, 5 mg between 1 and 4 years, 7.5 mg between 5 and 9 years, and 10 mg for 10-year-old children. The duration of administration of diazepam did not exceed 60 seconds. Duration N/A. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=234) Intervention 2: Drug - Lorazepam. Sublingual Lorazepam - was administered at a dose of 0.1 mg/kg of body weight. A 1 mg tablet was administered to children between 6 and 36 months old and 2.5 mg for those older than 4 years. Depending on the patient's condition, the tablet was placed under the tongue or between the cheek and gum. Duration N/A. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAZEPAM versus LORAZEPAM

Protocol outcome 1: Mortality (including SUDEP) at study endpoint
- Actual outcome: Mortality at N/A; Group 1: 12/202, Group 2: 7/234
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: causes -diazepam/lorazepam; Cerebral malaria - 119/154, Epilepsy - 28/22, Meningitis - 17/17; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at

study endpoint - Actual outcome: Seizure cessation within 5 min at 5 min; Group 1: 77/202, Group 2: 65/234 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: causes - diazepam/lorazepam; Cerebral malaria - 119/154, Epilepsy - 28/22, Meningitis - 17/17; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome: Seizure cessation within 10 min at 10 min; Group 1: 160/202, Group 2: 131/234 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: causes - diazepam/lorazepam; Cerebral malaria - 119/154, Epilepsy - 28/22, Meningitis - 17/17; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome: Seizure cessation within 20 min at 20 min; Group 1: 184/202, Group 2: 194/234 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: causes - diazepam/lorazepam; Cerebral malaria - 119/154, Epilepsy - 28/22, Meningitis - 17/17; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 3: Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours - Actual outcome: Seizure recurrence within 24 hours at 24 hours; Group 1: 80/202, Group 2: 85/234 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: causes - diazepam/lorazepam; Cerebral malaria - 119/154, Epilepsy - 28/22, Meningitis - 17/17; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Time to event seizure cessation at study endpoint; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint; Healthcare resource use at study endpoint

Study	**Mcintyre 2005[115]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=177)
Countries and setting	Conducted in United Kingdom; Setting: ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hour follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible children were those aged 6 months and older, who presented to the emergency of one of the four participating hospitals, still having a seizure, who did not already have established intravenous access. Children who had chronic epilepsy or who had been given prehospital emergency or rescue treatment were not excluded from the trial. It was anticipated that most seizures would be generalized tonic-clonic and it was not intended to include those patients with partial or non-convulsive seizures.
Exclusion criteria	Not stated.
Age, gender and ethnicity	Age - Median (IQR): 3 years (1 to 5 years). Gender (M:F): 98 male, 79 female. Ethnicity: Not stated.
Further population details	1. Age: Children 2. Non convulsive by type: N/A
Indirectness of population	No indirectness

Interventions	(n=92) Intervention 1: Drug - Midazolam. Buccal midazolam - the dose was determined by the child's age and was designed to give about 0.5 mg per kg (2.5 mg for children aged 6 to 12 months, 5 mg for 1 to 4 years, 7.5mg for 5-9 years, 10 mg for 10 years and older). The intravenous preparation of midazolam hydrochloride, filtered through a needle or straw, was administered into the buccal cavity between the gum and cheeks. Duration N/A. Concurrent medication/care: If the child was still having a seizure at 10 min and intravenous access had been established, then intravenous Lorazepam (100µg per kg) was administered, and any additional medication given based on each participating hospitals protocols or guidelines. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=85) Intervention 2: Drug - Diazepam. Rectal diazepam - the dose was determined by the child's age and was designed to give about 0.5 mg per kg (2.5 mg for children aged 6 to 12 months, 5 mg for 1 to 4 years, 7.5mg for 5-9 years, 10 mg for 10 years and older). Duration N/A. Concurrent medication/care: If the child was still having a seizure at 10 min and intravenous access had been established, then intravenous Lorazepam (100µg per kg) was administered, and any additional medication given based on each participating hospitals protocols or guidelines. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Academic or government funding (This study was funded by SEARCH, Derbyshire Children's Research Fund, and Alder Hey Children's Hospital Research fund.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus DIAZEPAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome: Therapeutic success (cessation of visible signs of seizure activity within 10 min of administration of the drug without respiratory depression and without another seizure within 1 hour) at 10 min; Group 1: 49/92, Group 2: 24/85
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: admission temperature midazolam/diazepam; 37.3/37.6; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A
- Actual outcome: Time (min) to stop seizing after treatment at N/A; midazolam - 10 (5-22)

diazepam - 15 (6-32) ; Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: admission temperature midazolam/diazepam; 37.3/37.6; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome: Stopped seizing within 10 min at 10 min; Group 1: 56/92, Group 2: 36/85 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: admission temperature midazolam/diazepam; 37.3/37.6; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 2: Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours - Actual outcome: Seizure recurrence at within 1 hour; Group 1: 7/56, Group 2: 12/31 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: admission temperature midazolam/diazepam; 37.3/37.6; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 3: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint - Actual outcome: Respiratory depression at N/A; Group 1: 4/92, Group 2: 6/85 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: admission temperature midazolam/diazepam; 37.3/37.6; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to event seizure cessation at study endpoint; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Misra 2006[126]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=68)
Countries and setting	Conducted in India; Setting: ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive patients with convulsive SE were recruited after approval from the local ethics committee. SE was defined as two or more convulsive seizures without full recovery of consciousness between the seizures or continuous convulsive seizures lasting for more than 10 min.
Exclusion criteria	Patients with non-convulsive and subtle SE, hypotension, cardiac arrhythmia, congestive heart failure, pregnancy, pancreatitis and drug allergy and those requiring immediate neurosurgery were excluded.
Age, gender and ethnicity	Age - Range: 12 participants aged 15 or under, 56 participants aged over 15. Age range 1 to 85 years. Gender (M:F): 41 male, 27 female. Ethnicity: Not stated.
Further population details	1. Age: adults and children 2. Non convulsive by type: N/A
Extra comments	

Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Drug - Valproate (sodium valproate / valproic acid). Sodium Valproate - this group received sodium valproate 30 mg/kg in 100 ml saline infused over 15 min. Duration 15 min. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=33) Intervention 2: Drug - Phenytoin. Phenytoin - This group received Phenytoin sodium 18 mg/kg in 100 ml saline infused immediately at a rate of 50 mg/min. Duration 15 min. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALPROATE (SODIUM VALPROATE / VALPROIC ACID) versus PHENYTOIN

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome for Convulsive status epilepticus : Clinical seizure cessation after infusion after 15 min at 15 min; Group 1: 23/35, Group 2: 14/33
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure duration: valproate - 1.76 (0.49), phenytoin - 1.70 (0.47), GCS score: valproate - 5.2 (0.9), phenytoin - 5.2 (1.2); Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Time to event seizure cessation at study endpoint
- Actual outcome for Convulsive status epilepticus : Seizure freedom in 24 hours at 24 hours; Group 1: 8/35, Group 2: 10/33
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure duration: valproate - 1.76 (0.49), phenytoin - 1.70 (0.47), GCS score: valproate - 5.2 (0.9), phenytoin - 5.2 (1.2); Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 3: Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours

- Actual outcome for Convulsive status epilepticus : Seizure recurrence within 24 hours at 24 hours; Group 1: 6/35, Group 2: 13/33 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure duration: valproate - 1.76 (0.49), phenytoin - 1.70 (0.47), GCS score: valproate - 5.2 (0.9), PHT - 5.2 (1.2); Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 4: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint - Actual outcome for Convulsive status epilepticus : Respiratory adverse events present at N/A; Group 1: 1/23, Group 2: 2/14 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure duration: valproate - 1.76 (0.49), phenytoin - 1.70 (0.47), GCS score: valproate - 5.2 (0.9), phenytoin - 5.2 (1.2); Group 1 Number missing: 12, Reason: Switched to other study drug; Group 2 Number missing: 19, Reason: Switched to other study drug.	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Misra 2012[125]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=79)
Countries and setting	Conducted in India; Setting: ED
Line of therapy	1st line
Duration of study	Intervention time: Up to 15 min
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Convulsive SE was defined as two or more convulsive seizures without full recovery of consciousness between the seizures or continuous convulsions lasting for more than 5 min. The patients were classified at the time of examination as generalized convulsive SE if easily visible generalized convulsions were present or subtle SE if coma and ictal discharges on EEG with subtle convulsive movements were present.
Exclusion criteria	Patients with non-convulsive SE, epilepsia partialis continua, pregnancy, drug allergy, history of taking the study drugs, and those requiring immediate neurosurgery were excluded.
Age, gender and ethnicity	Age - Mean (SD): lorazepam - 38.9 years (23.25), levetiracetam - 39.16 (21.16). Gender (M:F): 51 male, 28 female. Ethnicity: Not stated.
Further population details	1. Age: adults 2. Non convulsive by type: N/A

Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Drug - Lorazepam. Lorazepam - 0.1 mg/kg in 10 ml saline IV in 2–4 min. Duration 2 to 4 min. Concurrent medication/care: Pulse, blood pressure, respiration, agitation, or subsequent infections were monitored following the study drug infusion. Blood counts, serum bilirubin, transaminases, creatinine, and electrolytes were monitored. The patients received general care, fluid, electrolytes, calories, antipyretics for fever, and specific treatment for underlying cause. Those developing respiratory suppression with abnormal arterial blood gas analysis were artificially ventilated and those developing hypotension were treated with fluid and vasopressors. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=38) Intervention 2: Drug - Levetiracetam. Levetiracetam - 20 mg/kg infused in 15 min. Duration 15 min. Concurrent medication/care: Pulse, blood pressure, respiration, agitation, or subsequent infections were monitored following the study drug infusion. Blood counts, serum bilirubin, transaminases, creatinine, and electrolytes were monitored. The patients received general care, fluid, electrolytes, calories, antipyretics for fever, and specific treatment for underlying cause. Those developing respiratory suppression with abnormal arterial blood gas analysis were artificially ventilated and those developing hypotension were treated with fluid and vasopressors. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LORAZEPAM versus LEVETIRACETAM

Protocol outcome 1: Mortality (including SUDEP) at study endpoint
- Actual outcome for Convulsive status epilepticus : Mortality at N/A; Group 1: 9/21, Group 2: 10/23
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure duration (hours) - lorazepam - 11.19 (21.10) levetiracetam - 17.49 (24.68), GCS score lorazepam - 8.49 (3.27) levetiracetam 8.13 (3.57); Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint

- Actual outcome for Convulsive status epilepticus : Clinical cessation of SE within 30 min at 30 min; Group 1: 31/41, Group 2: 29/38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure duration (hours) - lorazepam - 11.19 (21.10) levetiracetam - 17.49 (24.68), GCS score lorazepam - 8.49 (3.27) levetiracetam 8.13 (3.57); Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 3: Time to event seizure cessation at study endpoint
- Actual outcome for Convulsive status epilepticus : Seizure freedom at 1 to 24 hours at 24 hour; Group 1: 21/41, Group 2: 23/38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure duration (hours) - lorazepam - 11.19 (21.10) levetiracetam - 17.49 (24.68), GCS score lorazepam - 8.49 (3.27) levetiracetam 8.13 (3.57); Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 4: Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours
- Actual outcome for Convulsive status epilepticus : Seizure recurrence within 1 to 24 hours at 24 hour; Group 1: 10/41, Group 2: 6/38
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure duration (hours) - lorazepam - 11.19 (21.10) levetiracetam - 17.49 (24.68), GCS score lorazepam - 8.49 (3.27) levetiracetam 8.13 (3.57); Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 5: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint
- Actual outcome for Convulsive status epilepticus : Hypotension at N/A; Group 1: 8/21, Group 2: 2/23
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure duration (hours) - lorazepam - 11.19 (21.10) levetiracetam - 17.49 (24.68), GCS score lorazepam - 8.49 (3.27) levetiracetam 8.13 (3.57); Group 1 Number missing: 20, Reason: Switched to other study drug; Group 2 Number missing: 15, Reason: Switched to other study drug
- Actual outcome for Convulsive status epilepticus : Respiratory failure at N/A; Group 1: 10/21, Group 2: 5/23
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure duration (hours) - lorazepam - 11.19 (21.10) levetiracetam - 17.49 (24.68), GCS score lorazepam - 8.49 (3.27) levetiracetam 8.13 (3.57); Group 1 Number missing: 20, Reason: Switched to other study drug; Group 2 Number missing: 15, Reason: Switched to other study drug

Protocol outcomes not reported by the study	Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Momen 2015[128]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in Iran; Setting: ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 60 min follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Enrolled children aged one month and older who were convulsing while attending our emergency departments.
Exclusion criteria	Excluded all those children who had one of the following criteria: those children with convulsive status seizures had an established IV access no arrival to our emergency departments, those children who were previously administered rectal or nasal benzodiazepines by parents or paramedics, all those whose parents were reluctant to give a verbal consent to participate in the study, and all those children having serial seizures without recovery of consciousness between seizures. Also excluded those children who had a history of serious adverse reactions to IM midazolam or rectal diazepam.
Age, gender and ethnicity	Age - Mean (SD): midazolam - 2 years (1.1), DIZ - 2.5 years (1.4). Gender (M:F): 58 male, 42 female. Ethnicity: Not stated.

Further population details	1. Age: Children 2. Non convulsive by type: N/A
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Drug - midazolam. Intramuscular midazolam - this was used with a dose of 0.3 mg/kg, injected into the left quadriceps muscle if the child was younger than 2 and if the child was older than 2, the left deltoid muscle was considered for injection. Duration N/A. Concurrent medication/care: All children who enrolled were admitted for at least 48 hours depending on the cause of seizures and the required investigations were conducted including: blood chemistry, EEG, CT or MRI. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=50) Intervention 2: Drug - Diazepam. Rectal Diazepam - a dose of 0.5mg/kg was given. It was drawn into a syringe, a tube was inserted into the rectum and the syringe was attached to the tube, following which the diazepam was expelled into the tube. To ensure the drug was administered correctly, the buttocks were held together 5 min to prevent expulsion and then the tube and the syringe were removed. Duration N/A. Concurrent medication/care: All children who enrolled were admitted for at least 48 hours depending on the cause of seizures and the required investigations were conducted including: blood chemistry, EEG, CT or MRI. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Academic or government funding (The Research Deputy of Ahvaz Jundishapur University of Medical Sciences - financial and logistic support (grant number U-91229).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus DIAZEPAM

Protocol outcome 1: Time to event seizure cessation at study endpoint
- Actual outcome for Convulsive status epilepticus : Medication treatment successful at N/A; Group 1: 48/50, Group 2: 47/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure aetiology midazolam/diazepam; febrile - 23/26, remote symptomatic - 15/10, idiopathic - 12/14; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours - Actual outcome for Convulsive status epilepticus : Seizure recurrence within 60 min after stopping motor activities at N/A; Group 1: 0/50, Group 2: 0/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure aetiology midazolam/diazepam; febrile - 23/26, remote symptomatic - 15/10, idiopathic - 12/14; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 3: Time to seizure recurrence after administration of monotherapy at study endpoint - Actual outcome for Convulsive status epilepticus : Time from arrival to stopping seizures at N/A; Mean; Median (range), Comments: midazolam - 127 seconds (83 to 320), diazepam - 243 (115 to 725) ; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure aetiology midazolam/diazepam; febrile - 23/26, remote symptomatic - 15/10, idiopathic - 12/14; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 4: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint - Actual outcome for Convulsive status epilepticus : Respiratory depression at N/A; Group 1: 0/50, Group 2: 0/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: seizure aetiology midazolam/diazepam; febrile - 23/26, remote symptomatic - 15/10, idiopathic - 12/14; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Mpimbaza 2008[130]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=330)
Countries and setting	Conducted in Uganda; Setting: ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive patients who were aged 3 months to 12 years and presented to the ACU while convulsing or experienced a seizure that lasted >5 min while in the unit were screened for enrolment. They had to fulfil the following criteria: 3 months to 12 years of age, no documented evidence of having received intravenous diazepam or intravenous phenobarbital within 24 hours before presentation, documented seizure persisting at the time of administration of the study drug and provision of informed consent to continue participation in the study.
Exclusion criteria	Not stated.
Age, gender and ethnicity	Age - Median (IQR): diazepam - 18 months (11.5 to 36), midazolam - 17 months (10.5 to 30). Gender (M:F): 166 male, 164 female. Ethnicity: Not stated.
Further population details	1. Age: children 2. Non convulsive by type: N/A

Indirectness of population	No indirectness
Interventions	(n=165) Intervention 1: Drug - Diazepam. Rectal placebo and buccal midazolam - Midazolam and buccal placebo were packaged in 2ml plastic syringes. Diazepam and rectal placebo were packaged in 2ml glass syringes. When due to receive treatment, the nurse opened the randomisation envelope and selected age-based dosages from the box with patients assigned treatment code. Both drugs were administered at ~0.5mg/kg (2.5 mg for 3-11 months, 5mg for 1-4 years, 7.5 for 5-9 years and 10mg for 10-12 years. For buccal treatments a syringe was placed between the teeth and cheek, the drug or placebo was administered, and the cheek was gently massaged. For rectal treatments the drug or placebo was administered via a tube inserted 3 to 4 cm into the rectum and the tube was flushed with air to ensure complete delivery of the drug. The buttocks were then held together for 5 min to prevent expulsion. Duration N/A. Concurrent medication/care: During a seizure oxygen was administered by nasal prongs. Peripheral oxygen saturation and blood pressure were recorded on study drug administration and at 5, 10, 20, 40 and 60 min thereafter. All children had a random blood sugar level determined with a Glucometer during the course of the study. Patients were followed for 24 hours after study drug administration. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=165) Intervention 2: Drug - Midazolam. Rectal placebo and buccal midazolam - Midazolam and buccal placebo were packaged in 2ml plastic syringes. Diazepam and rectal placebo were packaged in 2ml glass syringes. When due to receive treatment, the nurse opened the randomisation envelope and selected age-based dosages from the box with patients assigned treatment code. Both drugs were administered at ~0.5mg/kg (2.5 mg for 3-11 months, 5mg for 1-4 yrs., 7.5 for 5-9 years and 10mg for 10-12 years. For buccal treatments a syringe was placed between the teeth and cheek, the drug or placebo was administered, and the cheek was gently massaged. For rectal treatments the drug or placebo was administered via a tube inserted 3 to 4 cm into the rectum and the tube was flushed with air to ensure complete delivery of the drug. The buttocks were then held together for 5 min to prevent expulsion. Duration N/A. Concurrent medication/care: During a seizure oxygen was administered by nasal prongs. Peripheral oxygen saturation and blood pressure were recorded on study drug administration and at 5, 10, 20, 40 and 60 min thereafter. All children had a random blood sugar level determined with a Glucometer during the course of the study. Patients were followed for 24 hours after study drug administration. Indirectness: No indirectness

	Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Equipment / drugs provided by industry (This investigation received support from the Fogarty International Centre of the National Institutes of Health (grant D43 TWO1506). Financial support was also provided by the Nuffield Foundation, UK. Both study drugs were donated by Roche Products Limited, Nairobi, Kenya)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAZEPAM versus MIDAZOLAM

Protocol outcome 1: Mortality (including SUDEP) at study endpoint
- Actual outcome: Mortality at N/A; Group 1: 12/165, Group 2: 8/165
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Classification of convulsion, diazepam/midazolam; febrile - 115/121, generalised - 134/135, focal - 31/30; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome: Seizure cessation within 10 min at 10 min; Group 1: 114/165, Group 2: 125/165
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Classification of convulsion, diazepam/midazolam; febrile - 115/121, generalised - 134/135, focal - 31/30; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 3: Time to event seizure cessation at study endpoint
- Actual outcome: Median time to cessation of seizure at N/A; diazepam - 4.4 min (2.72 to 6.58)
midazolam - 4.8 min (3.02 to 6.52) ;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Classification of convulsion, diazepam/midazolam; febrile - 115/121, generalised - 134/135, focal - 31/30; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 4: Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours
- Actual outcome: Seizure recurrence in subsequent hour of initial control at 1 hour; Group 1: 20/114, Group 2: 10/125

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Classification of convulsion, diazepam/midazolam; febrile - 115/121, generalised - 134/135, focal - 31/30; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome: Seizure recurrence within 24 hours at 24 hours; Group 1: 51/110, Group 2: 47/120 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Classification of convulsion, diazepam/midazolam febrile - 115/121, generalised - 134/135, focal - 31/30; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 5: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint - Actual outcome: Respiratory depression at N/A; Group 1: 2/165, Group 2: 2/165 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Classification of convulsion, diazepam/midazolam; febrile - 115/121, generalised - 134/135, focal - 31/30; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study (subsidiary papers)	**Silbergleit 2012[187] (Silbergleit 2011[189], Welch 2015[239])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=893)
Countries and setting	Conducted in USA; Setting: ED
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Unclear: Welch - secondary analysis of the RAMPART clinical trial database focusing on patients younger than 18 years of age.
Inclusion criteria	The intended study population included children with an estimated body weight of 13 kg or more and adults requiring treatment with benzodiazepines for status epilepticus in the prehospital setting. Subjects were enrolled if they were having convulsive seizures at the time of treatment by paramedics and were reported by reliable witnesses to have been continuously convulsing for longer than 5 min or if they were having convulsive seizures at the time of treatment after having intermittent seizures without regaining consciousness for longer than 5 min.
Exclusion criteria	Subjects were excluded for the following reasons: the acute precipitant of the seizures was major trauma, hypoglycaemia, cardiac arrest, or a heart rate of less than 40 beats per min (since these conditions require alternative treatments); they had a known allergy to midazolam or lorazepam; they were known to be pregnant or a prisoner; they were being treated as part of another study; or, pre-emptively, they opted out of this study by wearing a medical-alert tag marked “RAMPART declined.”

Age, gender and ethnicity	Age - Mean (SD): midazolam - 43 (22), lorazepam - 44 (22). Gender (M:F): 488 male, 405 female. Ethnicity: 453 black, 348 white, 92 other
Further population details	1. Age: adults and children. 2. Non convulsive by type: N/A
Indirectness of population	No indirectness
Interventions	(n=448) Intervention 1: Drug - Midazolam. Midazolam - All adults and those children with an estimated body weight of more than 40 kg received 10 mg of intramuscular midazolam followed by intravenous placebo. In children with an estimated weight of 13 to 40 kg, the active treatment was 5 mg of intramuscular midazolam. Duration N/A. Concurrent medication/care: All subjects were treated with the intramuscular autoinjector, after which venous access was immediately achieved and treatment was administered by means of intravenous syringe. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=445) Intervention 2: Drug - Lorazepam. Lorazepam - All adults and those children with an estimated body weight of more than 40 kg received intramuscular placebo followed by 4 mg of intravenous lorazepam. In children with an estimated weight of 13 to 40 kg, the active treatment was 2 mg of intravenous lorazepam. Duration N/A. Concurrent medication/care: All subjects were treated with the intramuscular autoinjector, after which venous access was immediately achieved and treatment was administered by means of intravenous syringe. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Academic or government funding (Supported by awards from the National Institute of Neurological Disorders and Stroke (NINDS) (U01NS056975 and U01NS059041); the National Institutes of Health Office of the Director Counter ACT Program; and the Biomedical Advanced Research and Development Authority of the Assistant Secretary for Preparedness and Response)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus LORAZEPAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at

study endpoint
- Actual outcome for Convulsive status epilepticus : Seizure terminated before arrival in the emergency department, no rescue therapy given at within 24 hours; Group 1: 329/448, Group 2: 282/445
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: cause of SE midazolam/lorazepam; Noncompliance with or discontinuation of anticonvulsant therapy - 137/141, Idiopathic or breakthrough status epilepticus - 121/121, Coexisting condition that lowered seizure threshold - 33/29; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Convulsive status epilepticus : Seizure terminated before arrival in the emergency department at within 24 hours; Group 1: 41/60, Group 2: 43/60; Comments: sub group analysis - 60 in each arm
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: cause of SE midazolam/lorazepam; Noncompliance with or discontinuation of anticonvulsant therapy - 137/141, Idiopathic or breakthrough status epilepticus - 121/121, Coexisting condition that lowered seizure threshold - 33/29; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours
- Actual outcome for Convulsive status epilepticus : Recurrent seizure within 12 hours after ED arrival at within 12 hours; Group 1: 51/448, Group 2: 47/445
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: cause of SE midazolam/lorazepam; Noncompliance with or discontinuation of anticonvulsant therapy - 137/141, Idiopathic or breakthrough status epilepticus - 121/121, Coexisting condition that lowered seizure threshold - 33/29; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Length of ICU stay at study endpoint
- Actual outcome for Convulsive status epilepticus : Length of ICU stay - days at N/A; Group 1: mean 5.7 (SD 9.5); n=123, Group 2: mean 4.1 (SD 4.7); n=155
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: cause of SE midazolam/lorazepam; Noncompliance with or discontinuation of anticonvulsant therapy - 137/141, Idiopathic or breakthrough status epilepticus - 121/121, Coexisting condition that lowered seizure threshold - 33/29; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Length of hospital stay at study endpoint
- Actual outcome for Convulsive status epilepticus : Length of hospital stay - days at N/A; Group 1: mean 6.7 (SD 10); n=251, Group 2: mean 5.5 (SD 6.4); n=285

Risk of bias: All domain - Low Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: history of epilepsy - midazolam 293, lorazepam295, ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint - Actual outcome for Convulsive status epilepticus : Hypotension at N/A; Group 1: 12/448, Group 2: 13/445 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: cause of SE midazolam/lorazepam; Noncompliance with or discontinuation of anticonvulsant therapy - 137/141, Idiopathic or breakthrough status epilepticus - 121/121, Coexisting condition that lowered seizure threshold - 33/29; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to event seizure cessation at study endpoint; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Thakker 2013[215]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in India; Setting; Setting: ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 60 min
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Children between the ages of 1 month and 12 years who presented with acute motor seizures lasting for at least 10 min were eligible for inclusion in our study. Children with an ongoing motor seizure for at least 10 min were enrolled, assuming that spontaneous cessation of such a prolonged seizure was low; it was the least time it would take to reach the hospital and most emergency physicians would initiate anticonvulsive treatment after that time.
Exclusion criteria	We excluded children with established intravenous lines or those who had received anticonvulsants before admission.
Age, gender and ethnicity	Age - Mean (SD): midazolam - 3.84 years (2.93), diazepam - 3.97 years (3.33). Gender (M:F): 27 male, 23 female. Ethnicity: Not stated.
Further population details	1. Age: Children 2. Non convulsive by type: N/A

Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Drug - Midazolam. Midazolam - Intranasal midazolam (0.2 mg/kg). Midazolam solution (5 mg/ml) was dripped by syringe into both nostrils in equal doses, and an intravenous line was immediately introduced. Duration N/A. Concurrent medication/care: Seizures that did not stop within 5 min but were controlled within 10 min were defined as successful, but delayed control. Seizures which did not stop within 10 min were defined as treatment failures, and intravenous diazepam was given to the midazolam group and phenobarbital followed by phenytoin to the diazepam group. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=23) Intervention 2: Drug - Diazepam. Diazepam - Intravenous diazepam (0.3 mg/kg). Duration N/A. Concurrent medication/care: Seizures that did not stop within 5 min but were controlled within 10 min were defined as successful, but delayed control. Seizures which did not stop within 10 min were defined as treatment failures, and intravenous diazepam was given to the midazolam group and phenobarbital followed by phenytoin to the diazepam group. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus DIAZEPAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome: Time interval between cessation of seizure and giving drug at N/A; Group 1: mean 3.01 (SD 2.79); n=27, Group 2: mean 2.67 (SD 2.31); n=23
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: type of seizure, midazolam/diazepam; generalized tonic clonic - 14/16, Simple partial seizure - 6/5, Complex partial seizure - 4/1, Subtle convulsion - 3/1; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Time to event seizure cessation at study endpoint - Actual outcome: Responded to initial treatment (5 min) at N/A; Group 1: 18/27, Group 2: 15/23 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: type of seizure, midazolam/diazepam; generalized tonic clonic - 14/16, Simple partial seizure - 6/5, Complex partial seizure - 4/1, Subtle convulsion - 3/1; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 3: Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours - Actual outcome: Seizure recurrence after initial treatment at N/A; Group 1: 3/27, Group 2: 3/23 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: type of seizure, midazolam/diazepam; generalized tonic clonic - 14/16, Simple partial seizure - 6/5, Complex partial seizure - 4/1, Subtle convulsion - 3/1; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 4: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint - Actual outcome: Respiratory depression at N/A; Group 1: 0/27, Group 2: 1/23 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: type of seizure, midazolam/diazepam; generalized tonic clonic - 14/16, Simple partial seizure - 6/5, Complex partial seizure - 4/1, Subtle convulsion - 3/1; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Tonekaboni 2012[217]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=92)
Countries and setting	Conducted in Iran; Setting: Paediatric ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	The inclusion criteria dictated that the patients needed to fulfil the following criteria: (1) documented seizure persisting at the time of administration of anticonvulsant; (2) types of atonic, tonic and tonic-clonic seizures; (3) seizure lasting for more than 5 min.
Exclusion criteria	The exclusion criteria were: (1) patients who received intravenous diazepam or other benzodiazepines within 24 hours prior to presentation of the seizure; (2) previous history of narrow angle acute glaucoma; (3) doubt about the historical information given by patient's family.
Age, gender and ethnicity	Age - Mean (SD): 17.5 months (10.1). Gender (M:F): 51 male, 41 female. Ethnicity: Not stated
Further population details	1. Age: Children 2. Non convulsive by type: N/A
Indirectness of population	No indirectness

Interventions	(n=32) Intervention 1: Drug - Midazolam. Buccal midazolam - this was used with following doses: 2.5 mg for children aged 6-12 months, 5 mg for 1-4 years, 7.5 mg for 5-9 years, and 10 mg for 10 years or older. Buccal midazolam in the appropriate dose was drawn into a syringe. Children received buccal midazolam by placing the syringe between their teeth and cheek, and after drug administration the cheek was gently massaged. Duration N/A. Concurrent medication/care: In the event that the seizure remained uncontrolled within ten min after the first buccal midazolam or intravenous diazepam administration, either phenobarbital or phenytoin was used as the second line antiepileptic. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=60) Intervention 2: Drug - Diazepam. Diazepam - Intravenous diazepam was administered in a dosage of 0.3 mg/kg/dose and through an intravenous line as usual. Duration N/A. Concurrent medication/care: In the event that the seizure remained uncontrolled within ten min after the first buccal midazolam or intravenous diazepam administration, either phenobarbital or phenytoin was used as the second line antiepileptic. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus DIAZEPAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint
- Actual outcome: Overall controlled seizure within 10 min administration at within 10 min administration; Group 1: 22/32, Group 2: 42/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A
- Actual outcome: Time to seizure control after first dose at N/A; Group 1: mean 3.76 (SD 0.39); n=32, Group 2: mean 2.25 (SD 0.4); n=60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint - Actual outcome: Mild hypotension at N/A; Group 1: 7/32, Group 2: 9/60 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to event seizure cessation at study endpoint; Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

Study	**Treiman 1998[221]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=518)
Countries and setting	Conducted in USA; Setting: ED
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with generalized convulsive status epilepticus were randomly assigned to receive intravenous treatment with lorazepam, phenobarbital, phenytoin, or diazepam followed by phenytoin. The key criterion for study entry was evidence of overt or subtle generalized convulsive status epilepticus at the time of evaluation, regardless of prior drug treatment.
Exclusion criteria	Patients who had received treatment and whose seizures had stopped were not eligible for inclusion. Other exclusion criteria included status epilepticus of a type other than generalized convulsive, an age of less than 18 years, pregnancy, a neurologic emergency requiring immediate surgical intervention, and the presence of a specific contraindication to therapy with hydantoin, benzodiazepine, or barbiturate drugs. If patients with repeated episodes of generalized convulsive status epilepticus were inadvertently enrolled more than once, only the first episode was included in the analysis.

Age, gender and ethnicity	Age - Mean (SD): overt - 58.6 years (15.6), subtle - 62.0 years (15.1). Gender (M:F): 430 male, 88 female. Ethnicity: Not stated.
Further population details	1. Age: adults 2. Non convulsive by type: N/A
Extra comments	Overt generalized convulsive status epilepticus was defined as recurrent convulsions without complete recovery between seizures, and subtle generalized convulsive status epilepticus as the stage of generalized convulsive status when the patient is in continuous coma, but only subtle motor convulsions are seen. Patients were classified as having one of these two types of status epilepticus according to the following operational definitions. Overt generalized convulsive status epilepticus was considered present when there were two or more generalized convulsions, without full recovery of consciousness between seizures, or continuous convulsive activity for more than 10 min (treatment after 10 min of continuous seizure activity was considered essential to protect against neuronal and systemic damage from ongoing seizure activity). Subtle generalized convulsive status epilepticus was considered present when the patient had coma and ictal discharges on the electroencephalogram, with or without subtle convulsive movements (rhythmic twitching of the arms, legs, trunk, or facial muscles; tonic eye deviation; or nystagmoid eye jerking). If the investigator required an electroencephalogram to diagnose generalized convulsive status epilepticus, the patient was considered to have subtle generalized convulsive status epilepticus.
Indirectness of population	No indirectness
Interventions	(n=127) Intervention 1: Drug - Phenytoin. Phenytoin - administered at a rate of 1 ml per minute to produce the maximal rates of drug infusion. Duration N/A. Concurrent medication/care: Identical-appearing drug-treatment kits were prepared for each drug regimen, with each kit containing a first, a second, and a third treatment box. The first treatment box consisted of one Tubex syringe and five vials, labelled A through E. A nomogram, based on the patient's weight, was used to determine the volume of solution administered from the Tubex and from each vial to produce the desired dose without compromising the blinded nature of the study. The Tubex solution and the solution from vial A were injected simultaneously. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:

	(n=136) Intervention 2: Drug - Lorazepam. Lorazepam - was administered by means of Tubex injection at a maximal rate of 0.5 ml per min. Duration N/A. Concurrent medication/care: Identical-appearing drug-treatment kits were prepared for each drug regimen, with each kit containing a first, a second, and a third treatment box. The first treatment box consisted of one Tubex syringe and five vials, labelled A through E. A nomogram, based on the patient's weight, was used to determine the volume of solution administered from the Tubex and from each vial to produce the desired dose without compromising the blinded nature of the study. The Tubex solution and the solution from vial A were injected simultaneously. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location: (n=124) Intervention 3: Drug – Phenobarbital. Phenobarbital - administered at a rate of 1 ml per min to produce the maximal rates of drug infusion. Duration N/A. Concurrent medication/care: Identical-appearing drug-treatment kits were prepared for each drug regimen, with each kit containing a first, a second, and a third treatment box. The first treatment box consisted of one Tubex syringe and five vials, labelled A through E. A nomogram, based on the patient's weight, was used to determine the volume of solution administered from the Tubex and from each vial to produce the desired dose without compromising the blinded nature of the study. The Tubex solution and the solution from vial A were injected simultaneously. Indirectness: No indirectness Further details: 1. Dose: 2. Risk of bias of studies: 3. Route of administration: 4. Study location:
Funding	Equipment / drugs provided by industry (Supported by the Department of Veterans Affairs Medical Research Service Cooperative Studies Program (CSP 265). Lorazepam and dummy lorazepam Tubexes used in the study were donated by Wyeth–Ayerst Laboratories.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENYTOIN versus LORAZEPAM

Protocol outcome 1: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint
- Actual outcome: Hypotension at N/A; Group 1: 42/127, Group 2: 48/136; Comments: Phenytoin - overt - 101 27 people
subtle - 26 15 people
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Baseline details: causal factors of SE, overt/subtle (%); remote neurological cause - 69.5/34.3, acute neurological cause - 27.3/37.3, life threatening medical condition - 32/56.7, cardiopulmonary arrest - 6.3/38.1, toxic effects of drugs - 6.3/5.2, alcohol withdrawal - 6.5/0.7; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENYTOIN versus PHENOBARBITAL Protocol outcome 1: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint - Actual outcome: Hypotension at N/A; Group 1: 42/127, Group 2: 57/124 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: causal factors of SE, lorazepam vs phenobarbital; overt/subtle (%); remote neurological cause - 69.5/34.3, acute neurological cause - 27.3/37.3, life threatening medical condition - 32/56.7, cardiopulmonary arrest - 6.3/38.1, toxic effects of drugs - 6.3/5.2, alcohol withdrawal - 6.5/0.7; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LORAZEPAM versus PHENOBARBITAL Protocol outcome 1: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at study endpoint - Actual outcome: Hypotension at N/A; Group 1: 48/136, Group 2: 57/124; Comments: 97 overt - 25 39 subtle - 23 pheno - 91 overt (31 people), 33 subtle (26 people) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: lorazepam vs phenobarbital; causal factors of SE, overt/subtle (%); remote neurological cause - 69.5/34.3, acute neurological cause - 27.3/37.3, life threatening medical condition - 32/56.7, cardiopulmonary arrest - 6.3/38.1, toxic effects of drugs - 6.3/5.2, alcohol withdrawal - 6.5/0.7; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at study endpoint; Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, 1 to 24 hours, non-convulsive- up to 1 month at study endpoint; Time to event seizure cessation at study endpoint; Seizure recurrence < within less than 24 hours after administration of monotherapy at 24 hours; Time to seizure recurrence after administration of monotherapy at study endpoint; Quality of life at study endpoint; Length of ICU stay at study endpoint; Length of hospital stay at

	study endpoint; Mean Glasgow outcome scale (% difference in the means between the two groups at study endpoint; Healthcare resource use at study endpoint

D.2 Add on therapies

Study	Agarwal 2007[4]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in India; Setting: ED
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 12 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Prolonged seizure resistant to benzodiazepines
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	SE defined as continuous or repeated seizure activity for more than 5 min without recovery of consciousness
Exclusion criteria	Pregnant women, children less than 2 years of age, patients with hepatic encephalopathy or myoclonic status epilepticus, neurological emergency requiring immediate surgical intervention, contraindication to therapy with hydantoin, benzodiazepine, or barbiturate drugs.
Age, gender and ethnicity	Age - Mean (SD): Valproate group: 27.4 (16.8) years, Phenytoin group: 27 (15.1) years. Gender (M:F): Valproate group: 70% male, Phenytoin group: 64% male. Ethnicity: Not stated
Further population details	1. Age: Adults (Children and adults).
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Drug - Valproate (sodium valproate / valproic acid). Intravenous, 20 mg/kg . Duration Intravenous time. Concurrent medication/care: Earlier given IV diazepam in doses of 0.2 mg/kg at 2 mg/min up to a maximum of 20 mg . Indirectness: No indirectness Further details: 1. Dose: Define (20 mg/kg). 2. Non convulsive by type: Not stated / Unclear 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world

Study	Agarwal 2007[4]
	(n=50) Intervention 2: Drug - Phenytoin. Intravenous, 20 mg/kg. Duration Infusion time. Concurrent medication/care: Earlier given IV diazepam in doses of 0.2 mg/kg at 2 mg/min up to a maximum of 20 mg. Indirectness: No indirectness Further details: 1. Dose: Define (20 mg/kg). 2. Non convulsive by type: Not applicable (Convulsive) 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALPROATE (SODIUM VALPROATE / VALPROIC ACID) versus PHENYTOIN

Protocol outcome 1: Mortality (including SUDEP) at 7 days
- Actual outcome for Convulsive status epilepticus: Mortality at 7 days; Group 1: 4/50, Group 2: 4/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Aetiology of SE: AED withdrawal/noncompliance - valproate 24% vs phenytoin 28%, inflammatory granuloma - valproate 24% vs phenytoin 24%, CNS infections - valproate 20% vs phenytoin 24%, primary generalised seizure - valproate 16% vs phenytoin 12%; Group 1 Number missing: Group 2 Number missing:

Protocol outcome 2: Seizure recurrence greater than or less than 24 hours after administration of monotherapy
- Actual outcome for Convulsive status epilepticus: Seizure recurrence in less than 24 hours at Less than 12 hours; Group 1: 6/50, Group 2: 8/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Aetiology of SE: AED withdrawal/noncompliance - valproate 24% vs phenytoin 28%, inflammatory granuloma - valproate 24% vs phenytoin 24%, CNS infections - valproate 20% vs phenytoin 24%, primary generalised seizure - valproate 16% vs phenytoin 12%; Group 1 Number missing: Group 2 Number missing:

Protocol outcome 3: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance)
- Actual outcome for Convulsive status epilepticus: Hypotension. respiratory depression, mild elevation of SGPT at 7 days; Group 1: 4/50, Group 2: 8/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Aetiology of SE: AED withdrawal/noncompliance - valproate 24% vs phenytoin 28%, inflammatory granuloma - valproate 24% vs phenytoin 24%, CNS infections - valproate 20% vs phenytoin 24%, primary generalised seizure - valproate 16% vs phenytoin 12%; Group 1 Number missing: Group 2 Number missing:

Protocol outcome 4: Time to seizure cessation at 30 min

Study	Agarwal 2007[4]
- Actual outcome for Convulsive status epilepticus: Time to seizure cessation - 20 min at 20 min; Group 1: 44/50, Group 2: 42/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Aetiology of SE: AED withdrawal/noncompliance - valproate 24% vs phenytoin 28%, inflammatory granuloma - valproate 24% vs phenytoin 24%, CNS infections - valproate 20% vs phenytoin 24%, primary generalised seizure - valproate 16% vs phenytoin 12%; Group 1 Number missing: Group 2 Number missing:	
Protocol outcomes not reported by the study	Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)); Time to event seizure cessation; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

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2

Study	Amiri-nikpour 2018[8]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in Iran; Setting: ED/hospital
Line of therapy	2nd line
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Acute seizure
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Benzodiazepine resistant seizures defined as continuous generalised convulsive seizure lasting greater than 5 min or two or more discrete seizures during which patient didn't return to consciousness
Exclusion criteria	Pregnancy, younger than 18 years, history of liver disease, requiring emergency neurological invasive intervention. hypotension, pancreatitis, CHF, cardiac

Study	Amiri-nikpour 2018[8]
	arrhythmias, postanoxic SE, nonepileptic seizures, sensitivity to valproate or phenytoin
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): Valproate group 42.16 (15.94) years, phenytoin group 43.69 (17.60) years. Gender (M:F): Valproate group 24/31, phenytoin group 27/28. Ethnicity: Not stated
Further population details	1. Age: Adults
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Drug - Valproate (sodium valproate / valproic acid). Intravenous valproate, 30 mg/kg as loading dose and then 4-8 mg/kg every 8 hours up to 12 hours. Duration 12 hours. Concurrent medication/care: Previously benzodiazepines. Indirectness: No indirectness Further details: 1. Dose: Define (Intravenous valproate, 30 mg/kg as loading dose and then 4-8 mg/kg every 8 hours up to 12 hours). 2. Non convulsive by type: Not applicable (Convulsive). 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (n=55) Intervention 2: Drug - Phenytoin. Intravenous phenytoin, 20 mg/kg as loading dose and then 1.5 mg/kg every 8 hours up to 12 hours. Duration 12 hours. Concurrent medication/care: Previously benzodiazepines. Indirectness: No indirectness Further details: 1. Dose: Define (Intravenous phenytoin, 20 mg/kg as loading dose and then 1.5 mg/kg every 8 hours up to 12 hours). 2. Non convulsive by type: Not applicable (Convulsive). 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world
Funding	Academic or government funding (Research Council of Urmia, University of Medical Sciences, Urmia, Iran)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALPROATE (SODIUM VALPROATE / VALPROIC ACID) versus PHENYTOIN

Protocol outcome 1: Mortality (including SUDEP)
- Actual outcome for Convulsive status epilepticus: Mortality at 7 days; Group 1: 7/55, Group 2: 7/55
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	Amiri-nikpour 2018[8]
Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Valproate vs phenytoin: drug discontinuation 35% vs 33%, primary generalised seizures: 18% vs 18%, brain stroke: 15% vs 13%; Group 1 Number missing: Group 2 Number missing: Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome for Convulsive status epilepticus: Seizure cessation (SE controlled) at 7 days; Group 1: 43/55, Group 2: 39/55 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Valproate vs phenytoin: drug discontinuation 35% vs 33%, primary generalised seizures - 18% vs 18%, brain stroke 15% vs 13%; Group 1 Number missing: Group 2 Number missing: Protocol outcome 3: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) - Actual outcome for Convulsive status Hypotension, bradycardia, bradypnea, raised liver enzymes at 7 days; Group 1: 4/55, Group 2: 6/55 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Valproate vs phenytoin: drug discontinuation 35% vs 33%, primary generalised seizures - 18% vs 18%, brain stroke 15% vs 13%; Group 1 Number missing: Group 2 Number missing:	
Protocol outcomes not reported by the study	Time to event seizure cessation; Seizure recurrence greater than or less than 24 hours after administration of monotherapy; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

Study (subsidiary papers)	Chakravarthi 2015[36] (Chakravarthi 2014[37])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in India; Setting: ED/hospital

Study (subsidiary papers)	**Chakravarthi 2015[36] (Chakravarthi 2014[37])**
Line of therapy	2nd line
Duration of study	Other: At discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Seizure
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Continuous, generalised, convulsive seizure lasting >5 min, failed to improve on lorazepam
Exclusion criteria	Already taking study drug, prior allergy to study drug, drug withdrawal seizures
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 35.41 (16.03) years. Gender (M:F): 25/19. Ethnicity: Not stated
Further population details	1. Age: Adults (Adults and children (range 14 to 75 years)).
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Drug - Levetiracetam. Intravenous 20 mg/kg (rate 100 mg/min) then maintenance dose. Duration 24 hours. Concurrent medication/care: Previously intravenous lorazepam 0.1 mg/kg at 1 mg/min. Indirectness: No indirectness Further details: 1. Dose: Define 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (n=22) Intervention 2: Drug - Phenytoin. Intravenous 20 mg/kg (maximum rate 50 mg/min) then maintenance dose. Duration 24 hours. Concurrent medication/care: Previously intravenous lorazepam 0.1 mg/kg at 1 mg/min. Indirectness: No indirectness Further details: 1. Dose: Define (Intravenous 20 mg/kg (maximum rate 50 mg/min) then maintenance dose). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LEVETIRACETAM versus PHENYTOIN	

Study (subsidiary papers)	Chakravarthi 2015[36] (Chakravarthi 2014[37])
Protocol outcome 1: Mortality (including SUDEP) - Actual outcome: Mortality at 24 hours; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Levetiracetam vs phenytoin: past history of epilepsy - 66% vs 76%, GCSE - n=20 vs n=21, FCSE - n=2 vs n=1; Group 1 Number missing: Group 2 Number missing: Protocol outcome 2: Seizure recurrence greater than or less than 24 hours after administration of monotherapy - Actual outcome: Seizure recurrence with 24 hours at 24 hours; Group 1: 9/22, Group 2: 6/22 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Levetiracetam vs phenytoin: past history of epilepsy - 66% vs 76%, GCSE - n=20 vs n=21, FCSE - n=2 vs n=1; Group 1 Number missing: Group 2 Number missing: Protocol outcome 3: Quality of life - Actual outcome: Good functional independence measure (FIM) at 24 hours; Group 1: 19/22, Group 2: 18/22 Risk of bias: All domain - High, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Levetiracetam vs phenytoin: past history of epilepsy - 66% vs 76%, GCSE - n=20 vs n=21, FCSE - n=2 vs n=1; Group 1 Number missing: Group 2 Number missing: Protocol outcome 4: Time to seizure cessation at 30 min - Actual outcome: Time to seizure cessation at 30 min; Group 1: 13/22, Group 2: 15/22 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Levetiracetam vs phenytoin: past history of epilepsy - 66% vs 76%, GCSE - n=20 vs n=21, FCSE - n=2 vs n=1; Group 1 Number missing: Group 2 Number missing:	
Protocol outcomes not reported by the study	Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)): Time to event seizure cessation; Time to seizure recurrence after administration of monotherapy; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance); Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

1

Study	Chen 2011[42]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in China; Setting: ED/hospital
Line of therapy	2nd line
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Seizure
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Diazepam resistant after 2 doses, 5 min of continuous seizure or repeated seizure without full recovery of consciousness or repeated seizure lasting for 30 min without recovery of consciousness,
Exclusion criteria	Unstable vital signs, liver dysfunction, requirement of immediate surgical intervention, hypersensitivity to study drugs, pregnancy or breast feeding
Age, gender and ethnicity	Age - Mean (SD): 41 (21) years. Gender (M:F): 36/30. Ethnicity: Not Stated
Further population details	1. Age: Adults (Adults and children).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Drug - Valproate (sodium valproate / valproic acid). Intravenous valproate at a loading dose of 30 mg/kg at a rate of 6 mg/kg per min followed by a continuous infusion at a rate of 1-2 mg/kg per hour maintained for at least 6 h after the control of the last seizure and then gradually tapered over 24 h. Duration 24 hours. Concurrent medication/care: Previously intravenous diazepam (0.2 mg/kg) twice at a 10-min interval. Indirectness: No indirectness Further details: 1. Dose: Define (Intravenous valproate at a loading dose of 30 mg/kg at a rate of 6 mg/kg per min followed by a continuous infusion at a rate of 1-2 mg/kg per hour maintained for at least 6 hours after the control of the last seizure and then gradually tapered over 24 hours). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: Low risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (n=36) Intervention 2: Drug - Diazepam. Diazepam bolus of 0.2mg/kg then a following infusion at an initial rate of 4 mg/h, the rate was maintained every 3 min by 1 microgram/kg per min until seizures were controlled or a maximum duration of 1 hour. Duration 1 hour. Concurrent medication/care: Previously intravenous

Study	Chen 2011[42]
	diazepam (0.2 mg/kg) twice at a 10-min interval. Indirectness: No indirectness Further details: 1. Dose: Define (Diazepam bolus of 0.2mg/kg then a following infusion at an initial rate of 4 mg/h, the rate was maintained every 3 min by 1 microgram/kg per min until seizures were controlled or a maximum duration of 1 hour). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: Low risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world
Funding	Academic or government funding (Capital Medicine development Committee Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALPROATE (SODIUM VALPROATE / VALPROIC ACID) versus DIAZEPAM

Protocol outcome 1: Mortality (including SUDEP)
- Actual outcome for Convulsive status epilepticus : Mortality at discharge; Group 1: 5/30, Group 2: 2/35
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Diazepam vs valproate: epilepsy related seizure - 36% vs 33%, viral encephalitis - 28% vs 40%, CVD - 14% vs 17%; Group 1 Number missing: Group 2 Number missing:

Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive))
- Actual outcome for Convulsive status epilepticus : Seizure cessation at 1 hour; Group 1: 15/30, Group 2: 20/36
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Diazepam vs valproate: epilepsy related seizure - 36% vs 33%, viral encephalitis - 28% vs 40%, CVD - 14% vs 17%; Group 1 Number missing: Group 2 Number missing:

Protocol outcome 3: Seizure recurrence greater than or less than 24 hours after administration of monotherapy
- Actual outcome for Convulsive status epilepticus: Seizure recurrence at Within 24 hours; Group 1: 3/15, Group 2: 5/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Diazepam vs valproate: epilepsy related seizure - 36% vs 33%, viral encephalitis - 28% vs 40%, CVD - 14% vs 17%; Group 1 Number missing: Group 2 Number missing:

Protocol outcome 4: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance)
- Actual outcome for Convulsive status epilepticus: Hypotension at 6 hours; Group 1: 0/30, Group 2: 2/36
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Chen 2011[42]
- Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Diazepam vs valproate: epilepsy related seizure - 36% vs 33%, viral encephalitis - 28% vs 40%, CVD - 14% vs 17%; Group 1 Number missing: Group 2 Number missing: - Actual outcome for Convulsive status epilepticus: Need for intubation at 6 hours; Group 1: 0/30, Group 2: 2/36 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Diazepam vs valproate: epilepsy related seizure - 36% vs 33%, viral encephalitis - 28% vs 40%, CVD - 14% vs 17%; Group 1 Number missing: Group 2 Number missing:	
Protocol outcomes not reported by the study	Time to event seizure cessation; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

1

Study	Chitsaz 2013[43]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Iran; Setting: ED
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Minimum age of 10 years, and the maximum age of 70 years, lack of evidence on substance abuse and addiction, no history of any cardiac, renal, or hepatic disorders, no history of absence, myoclonic, atonic, or non-convulsive seizures (according to the history obtained from the companions), no history of metabolic disorders causing seizures, no history of allergy to phenytoin and sodium valproate, no history of cardiac arrhythmias, no evidence of pregnancy, and no history of phenytoin consumption in the individuals whose treatment had been began with

Study	Chitsaz 2013[43]
	sodium valproate
Exclusion criteria	Not receiving the full dose of medication for any reason, and the existence of metabolic disorders causing seizures during the diagnostic evaluation Not receiving the full dose of medication for any reason, and the existence of metabolic disorders causing seizures during the diagnostic evaluation
Age, gender and ethnicity	Age - Mean (SD): Valproate 47.4 (14) years, phenytoin 45.5 (20.4) years. Gender (M:F): 18/12. Ethnicity: Not stated
Further population details	1. Age: Adults (Adults and children).
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Drug - Valproate (sodium valproate / valproic acid). Intravenous sodium valproate: initial bolus of 20 mg/kg infused within 10 min, and half an hour after this loading, continuous infusion at a rate of 1 mg/kg/hour as maintenance dose within 24 hour Duration 24 h. Concurrent medication/care: Previously diazepam. Indirectness: No indirectness Further details: 1. Dose: Define (Intravenous sodium valproate: initial bolus of 20 mg/kg). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: (n=15) Intervention 2: Drug - Phenytoin. initial bolus of 20 mg/kg and at a rate of 50 mg/min (25 mg/min for older patients), then maintenance dose of 4.5 mg/kg/h for 24 hours. Duration 24 h. Concurrent medication/care: Previously diazepam. Indirectness: No indirectness Further details: 1. Dose: Define (initial bolus of 20 mg/kg and at a rate of 50 mg/min (25 mg/min for older patients), then maintenance dose of 4.5 mg/kg/hour for 24 hours). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location:

Study	Chitsaz 2013[43]
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALPROATE (SODIUM VALPROATE / VALPROIC ACID) versus PHENYTOIN Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome for Convulsive status epilepticus: Seizure cessation within 1 hour at 1 hour; Group 1: 11/15, Group 2: 9/15 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality (including SUDEP) ; Time to event seizure cessation; Seizure recurrence greater than or less than 24 hours after administration of monotherapy; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance); Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

Study (subsidiary papers)	ConSEPT trial: Dalziel 2019[46] (Dalziel 2017[47])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=238)
Countries and setting	Conducted in Australia, New Zealand; Setting: ED
Line of therapy	2nd line
Duration of study	Follow up (post intervention): Primary outcome: 5 min after treatment

Study (subsidiary papers)	ConSEPT trial: Dalziel 2019[46] (Dalziel 2017[47])
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Convulsive SE as defined as being unresponsive with continuing abnormality of movement for longer than 5 min, or 2 or more recurrent convulsions without recovery of consciousness between seizures, or 3 or more convulsions within the previous hour and a current convulsion
Exclusion criteria	On regular phenytoin and levetiracetam, administered second-line anticonvulsants (phenytoin, levetiracetam, phenobarbitone or paraldehyde) in the past 24 hours, management plan stating refractory to phenytoin or levetiracetam, SE due to head injury or eclampsia
Age, gender and ethnicity	Age - Mean (range): 3.9 (3.8) years. Gender (M:F): 112/121. Ethnicity: Not stated
Further population details	1. Age: Children
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=114) Intervention 1: Drug - Phenytoin. 20 mg/kg infusion over 20 min (50 mg/ml phenytoin; 0.9% sodium chloride to a maximum volume of 20 ml). Duration 20 min. Concurrent medication/care: All patients initially treated 2 doses of benzodiazepines. Indirectness: No indirectness Further details: 1. Dose: Define (20 mg/kg). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: Low risk of bias 4. Route of administration: intravenous (and intraosseous). 5. Study location: Rest of the world (n=119) Intervention 2: Drug - Levetiracetam. 40 mg/kg infusion over 20 min (maximum 1 g, diluted 1.4 with 0.9% sodium chloride to a maximum of 20 ml). Duration 20 min. Concurrent medication/care: Patients initially treated 2 doses of benzodiazepines. Indirectness: No indirectness Further details: 1. Dose: Define (20 mg/kg). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: Low risk of bias 4. Route of administration: intravenous (and intraosseous). 5. Study location: Rest of the world

Study (subsidiary papers)	ConSEPT trial: Dalziel 2019[46] (Dalziel 2017[47])
Funding	Academic or government funding (Health Research Council of New Zealand, A+ Trust, Emergency Medicine Foundation, Townsville Hospital, Private Practice Fund, Eric Ormond Baker Charitable Fund, and Princess Margaret Hospital Foundation).
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENYTOIN versus LEVETIRACETAM Protocol outcome 1: Mortality (including SUDEP) - Actual outcome for Convulsive status epilepticus: Mortality at 27 days; Group 1: 1/114, Group 2: 0/119 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Phenytoin vs levetiracetam: febrile 72% vs 73%, focal onset 12 % vs 12% ; Group 1 Number missing: Group 2 Number missing: Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome for Convulsive status epilepticus: Seizure cessation within 5 min at 5 min; Group 1: 68/114, Group 2: 60/119 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Phenytoin vs levetiracetam: febrile 72% vs 73%, focal onset 12 % vs 12% ; Group 1 Number missing: Group 2 Number missing: - Actual outcome for Convulsive status epilepticus: Seizure cessation within 2 hours at 2 h; Group 1: 62/114, Group 2: 61/119 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Phenytoin vs levetiracetam: febrile 72% vs 73%, focal onset 12 % vs 12% ; Group 1 Number missing: Group 2 Number missing: Protocol outcome 3: Length of ICU stay - Actual outcome for Convulsive status epilepticus: Length of ICU stay at Hospital admission; Group 1: 20/114, Group 2: 33/119; Comments: Phenytoin- Median (range): 20 (14-29) days, levetiracetam- Median (range): 33 (22-61) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Phenytoin vs levetiracetam: febrile 72% vs 73%, focal onset 12 % vs 12%; Group 1 Number missing: Group 2 Number missing:	
Protocol outcomes not reported by the study	Time to event seizure cessation; Seizure recurrence greater than or less than 24 hours after administration of monotherapy; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of hospital stay; mean

Study (subsidiary papers)	ConSEPT trial: Dalziel 2019[46] (Dalziel 2017[47])
	Glasgow outcome scale (% difference in the means between the two groups; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance); Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

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Study	Dr. senthil kumar 2018[179]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in India; Setting: Raja Mirasudar Hospital attached to Thanjavur Medical College, Thanjavur, South India.
Line of therapy	2nd line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Children between 3 months and 12 years who presented to paediatric emergency department with convulsive status epilepticus and who were still seizing after two doses of benzodiazepines (diazepam/ lorazepam/ midazolam) administered by one of the following route (rectal/ buccal/ intranasal/ intravenous/intramuscular) at the recommended dose were included in the study.
Exclusion criteria	Children on regular oral phenytoin and levetiracetam use, CSE due to an obvious major head injury, known contraindication or allergy to levetiracetam or fosphenytoin, administration of second line anticonvulsant (phenytoin, fosphenytoin, phenobarbitone, sodium valproate) in the previous 24 hours, previous randomization and who were discharged against medical advice were excluded from the study.
Age, gender and ethnicity	Age - Mean (SD): LEV: 2.28 + 2.19; FPHT: 3.34 + 3.36. Gender (M:F): 34/15. Ethnicity: Not stated

Study	Dr. senthil kumar 2018[179]
Further population details	1. Age: Children
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Drug - Levetiracetam. 30mg/kg of LEV infusion over 7 minutes diluted 1:1 with 0.9% sodium chloride to a minimum volume of 10ml. Duration administered over 7 minutes. Concurrent medication/care: two previous administrations of two doses of benzodiazepines (diazepam/ lorazepam/ midazolam) administered by one of the following route (rectal/ buccal/ intranasal/intravenous/intramuscular). Indirectness: No indirectness Further details: 1. Dose: Define (30mg/kg). 2. Non convulsive by type: Not stated / Unclear (convulsive status epilepticus). 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous (IV administration). 5. Study location: Rest of the world (India). (n=25) Intervention 2: Drug - Fosphenytoin. 20mg/kg PE of FPHT diluted 1 in 4 with 0.9% sodium chloride to a minimum volume of 20ml. Duration administered over 7 minutes. Concurrent medication/care: two previous administrations of two doses of benzodiazepines (diazepam/ lorazepam/ midazolam) administered by one of the following route (rectal/ buccal/ intranasal/intravenous/intramuscular). Indirectness: No indirectness Further details: 1. Dose: Define (20mg/kg). 2. Non convulsive by type: Not stated / Unclear (convulsive status epilepticus). 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (India).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LEVETIRACETAM versus FOSPHENYTOIN Protocol outcome 1: Time to event seizure cessation - Actual outcome for Convulsive status epilepticus: Time taken to terminate seizures (minutes) at after administration of medication; Group 1: mean 3.3 MINUTES (SD 1.16); n=25, Group 2: mean 2.5 MINUTES (SD 1.4); n=25; Comments: p value 0.029 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Seizure recurrence greater than or less than 24 hours after administration of monotherapy - Actual outcome for Convulsive status epilepticus: Seizure recurrence at after administration of medication; Group 1: 5/25, Group 2: 3/25; Comments: Numbers of events calculated from percentages LEV: 17.5% and FPHT: 9.5% and rounded to whole number	

Study	Dr. senthil kumar 2018[179]
p value 0.44 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of ICU stay - Actual outcome for Convulsive status epilepticus: PICU stay (hours) at after admission; Group 1: mean 44 hours (SD 26.7); n=25, Group 2: mean 42.3 hours (SD 65.1); n=25; Comments: p value 0.105 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Length of hospital stay - Actual outcome for Convulsive status epilepticus: Length of hospital stay (days) at after admission; Group 1: mean 6.3 days (SD 3.7); n=25, Group 2: mean 5.8 days (SD 4.9); n=25; Comments: p value 0.311 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) - Actual outcome for Convulsive status epilepticus: Respiratory Depression at after admission; Group 1: 0/25, Group 2: 2/25 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Time to seizure cessation at 5 min - Actual outcome for Convulsive status epilepticus: Cessation of seizures (within 5 minutes) at 5 minutes; Group 1: 23/25, Group 2: 21/25 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality (including SUDEP) ; Time to seizure cessation, (5 minutes after drug administration, 10 mins, 30 mins, 60 mins, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)): Time to seizure recurrence after administration of monotherapy; Quality of life; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 1 month; Time to

Study	Dr. senthil kumar 2018[179]
	seizure cessation at 10 min; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at ≤ 24 hours

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Study	ESETT trial: Kapur 2019[75]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=384)
Countries and setting	Conducted in USA; Setting: Patients were enrolled at 57 hospital emergency departments across the United States.
Line of therapy	2nd line
Duration of study	Intervention + follow up: 30 days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible for participation if they were 2 years of age or older, had been treated with a generally accepted cumulative dose of benzodiazepines for generalized convulsive seizures lasting more than 5 min, and continued to have persistent or recurrent convulsions in the emergency department at least 5 min after the last dose of benzodiazepine (to provide sufficient time for the drug at this dose to act) and no more than 30 min after the last dose of benzodiazepine (to avoid enrolling patients for whom re-administration of benzodiazepines would have been appropriate). The seizure and its initial treatment with benzodiazepines could occur before the patient's arrival in the emergency department. The minimal adequate cumulative doses of benzodiazepines were defined as diazepam at a dose of 10 mg (administered intravenously or rectally), lorazepam at a dose of 4 mg (administered intravenously), or midazolam at a dose of 10 mg (administered intravenously or intramuscularly) for all adults and for children with a body weight of at least 32 kg; and diazepam at a dose of 0.3 mg/kg of body weight (administered intravenously or rectally), lorazepam at a dose of 0.1 mg/kg (administered intravenously), or midazolam at a dose of 0.3 mg/kg (administered intramuscularly) or 0.2 mg/kg (administered intravenously) for children who weighed less than 32 kg. These drugs may have been administered in divided doses, including before the patient's arrival in the emergency department.

Study	ESETT trial: Kapur 2019[75]
Exclusion criteria	Patients were excluded from the trial for the following reasons, as determined on arrival in the emergency department: the acute precipitant of seizure was major trauma, hypoglycaemia, hyperglycaemia, cardiac arrest, or postanoxia; the patient was pregnant or incarcerated; or the patient pre-emptively opted out of this trial by wearing a medical alert tag marked “ESETT declined” (these tags were made available by the trial when requested). Patients were also excluded if they had already been treated for the current episode of status epilepticus with anticonvulsant agents other than benzodiazepines or if the trachea was intubated. We excluded patients with known allergy or contraindications to any of the trial drugs, including known inborn metabolic disorder, liver disease, or severe renal impairment.
Age, gender and ethnicity	Age - Mean (SD): Levetiracetam 33.3 (26.0) years, fosphenytoin 32.8 (25.4) years, valproate 32.2 (25.4) years. Gender (M:F): 213 male, 171 female. Ethnicity: 165 Black, 160 White, 59 other
Further population details	1. Age:
Indirectness of population	No indirectness
Interventions	(n=118) Intervention 1: Drug - Fosphenytoin. Fosphenytoin - Trial drug vial contained 16.66 mg Phenytoin equivalents [mgPE]/ml. The weight-based infusion rate provided fosphenytoin at a dose of 20 mgPE per kilogram (maximum, 1500 mgPE). Trial drugs were identical in appearance, formulation, packaging, and administration, including the total volume in the vial and duration of infusion. After 10 min, the infusion of the trial drug was discontinued. Duration N/A. Concurrent medication/care: Rescue therapy was given as clinically determined by the care team for persistent or recurrent seizures after 20 min from the start of trial-drug infusion. Unmasking of the trial drug for purposes of patient care, after determination of the primary outcome at 60 min, was allowed, but emergency unblinding (before 60 min) was considered a protocol deviation. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location: (n=145) Intervention 2: Drug - Levetiracetam. Levetiracetam - Trial-drug vials contained levetiracetam (50 mg/ml). The weight-based infusion rate provided levetiracetam at a dose of 60 mg per kilogram (maximum, 4500 mg). Trial drugs were identical in appearance, formulation, packaging, and administration, including the total volume in the vial and duration of infusion. After 10 min, the infusion of the

Study	ESETT trial: Kapur 2019[75]
	trial drug was discontinued. Duration N/A. Concurrent medication/care: Rescue therapy was given as clinically determined by the care team for persistent or recurrent seizures after 20 min from the start of trial-drug infusion. Unmasking of the trial drug for purposes of patient care, after determination of the primary outcome at 60 min, was allowed, but emergency unblinding (before 60 min) was considered a protocol deviation. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: not applicable 3. Risk of bias of studies: 4. Route of administration: 5. Study location: (n=121) Intervention 3: Drug - Valproate (sodium valproate / valproic acid). Valproate - Trial-drug vials contained valproate (33.33 mg/ml). The weight-based infusion rate provided valproate at a dose of 40 mg/kg (maximum, 3000 mg). Trial drugs were identical in appearance, formulation, packaging, and administration, including the total volume in the vial and duration of infusion. After 10 min, the infusion of the trial drug was discontinued. Duration N/A. Concurrent medication/care: Rescue therapy was given as clinically determined by the care team for persistent or recurrent seizures after 20 min from the start of trial-drug infusion. Unmasking of the trial drug for purposes of patient care, after determination of the primary outcome at 60 min, was allowed, but emergency unblinding (before 60 min) was considered a protocol deviation. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: not applicable3. Risk of bias of studies: 4. Route of administration: 5. Study location:
Funding	Academic or government funding (Funded by the National Institute of Neurological Disorders and Stroke; ESETT ClinicalTrials.gov number, NCT01960075)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOSPHENYTOIN versus LEVETIRACETAM

Protocol outcome 1: Mortality (including SUDEP)
- Actual outcome: Mortality at 30 days; Group 1: 3/125, Group 2: 7/150
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Study	ESETT trial: Kapur 2019[75]
Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome: Seizure cessation (and improvement in consciousness at 60 min without other anticonvulsant medications) at 60 min; Group 1: 53/118, Group 2: 68/145 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 3: Time to event seizure cessation - Actual outcome: Median time from start of trial drug infusion to termination of seizures for patients with treatment success (IQR) min at N/A; Mean; Median (IQR) min, Comments: levetiracetam = 10.5 (5.7 - 15.5), fosphenytoin = 11.7 (7.5 - 20.9), valproate = 7 (4.6 - 14.9); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 4: Seizure recurrence greater than or less than 24 hours after administration of monotherapy - Actual outcome: Seizure recurrence 60 min to 12 hours after start of trial drug infusion at 60 min to 12 hours; Group 1: 14/125, Group 2: 16/150 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 5: Length of ICU stay - Actual outcome: ICU admission at 30 days; Group 1: 70/118, Group 2: 87/145 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome: Median length of ICU stay at N/A; levetiracetam = 1 (0-3), fosphenytoin = 1 (0-3), valproate = 1 (0-3) ; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status	

Study	ESETT trial: Kapur 2019[75]
epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 6: Length of hospital stay - Actual outcome: Median length of hospital stay at N/A; LEV = 3 (1 -7) FOS = 3 (1-6) VAL = 3 (2-6); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 7: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) - Actual outcome: Respiratory depression at 30 days; Group 1: 16/125, Group 2: 12/150 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome: Hypotension within 60 min of starting trial at 60 min; Group 1: 4/125, Group 2: 1/150 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOSPHENYTOIN versus VALPROATE (SODIUM VALPROATE / VALPROIC ACID) Protocol outcome 1: Mortality (including SUDEP) - Actual outcome: Mortality at 30 days; Group 1: 3/125, Group 2: 2/125 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive))

Study	ESETT trial: Kapur 2019[75]
- Actual outcome: Seizure cessation (and improvement in consciousness at 60min without other anticonvulsant medications) at 60 min; Group 1: 53/118, Group 2: 56/121 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 3: Seizure recurrence greater than or less than 24 hours after administration of monotherapy - Actual outcome: Seizure recurrence 60 min to 12 hours after start of trial drug infusion at 60 min to 12 hours; Group 1: 14/125, Group 2: 14/125 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 4: Length of ICU stay - Actual outcome: ICU admission at 30 days; Group 1: 70/118, Group 2: 71/121 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 5: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) - Actual outcome: Respiratory depression at 30 days; Group 1: 16/125, Group 2: 10/125 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome: Hypotension within 60 min of starting trial at 60 min; Group 1: 4/125, Group 2: 2/125 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LEVETIRACETAM versus VALPROATE (SODIUM VALPROATE / VALPROIC ACID)	

Study	ESETT trial: Kapur 2019[75]
Protocol outcome 1: Mortality (including SUDEP) - Actual outcome: Mortality at 30 days; Group 1: 7/150, Group 2: 2/125 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis LEV/FOS/VAL (%); seizure or status epilepticus - 88.3%/88.1%/84.3%, non-epileptic spell - 9%/9.3%/10.7%, unable to adjudicate - 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome: Seizure cessation (and improvement in consciousness at 60min without other anticonvulsant medications) at 60 min; Group 1: 68/145, Group 2: 56/121 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 3: Seizure recurrence greater than or less than 24 hours after administration of monotherapy - Actual outcome: Seizure recurrence 60 min to 12 hours after start of trial drug infusion at 60 min to 12 hours; Group 1: 16/150, Group 2: 14/125 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 4: Length of ICU stay - Actual outcome: ICU admission at 30 days; Group 1: 87/145, Group 2: 71/121 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 5: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) - Actual outcome: Respiratory depression at 30 days; Group 1: 12/150, Group 2: 10/125 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	

Study	ESETT trial: Kapur 2019[75]
- Actual outcome: Hypotension within 60 min of starting trial at 60 min; Group 1: 1/150, Group 2: 2/125 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: final diagnosis levetiracetam/fosphenytoin/valproate (%); seizure or status epilepticus: 88.3%/88.1%/84.3%, non-epileptic spell: 9%/9.3%/10.7%, unable to adjudicate: 2.8%/2.5%/5%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Time to seizure recurrence after administration of monotherapy; Quality of life; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

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Study	Fallah 2007[55]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Iran; Setting: ICU
Line of therapy	2nd line
Duration of study	--:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Children admitted to the ICU with refractory convulsive status epilepticus
Exclusion criteria	Liver or kidney dysfunction, hypotension, cardia arrhythmia or block electrolyte abnormalities, second admission with status epilepticus
Age, gender and ethnicity	Age - Mean (range): 3.8 (0.1 to 12) years. Gender (M:F): 9/11. Ethnicity: Not stated
Further population details	1. Age: Children
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Drug - Other. Lignocaine

Study	Fallah 2007[55]
	Intravenous lignocaine: initial dose of 1 mg/kg intravenously at a rate of 25 mg/min, a second bolus of 1 mg/kg was infused if no response or seizure recurred, if seizures did not stop after 2nd dose and within 15 min, continuous lignocaine infusion of 1 mg/kg/h, if still ineffective, lignocaine was infused with the same dose and then decreased by 0.5 mg/kg/h every hour until cessation . Duration Immediately. Concurrent medication/care: Previously: intravenous diazepam (0.2 to 0.3 mg/kg) which was repeated after 5 if seizure reoccurred, this was followed by phenytoin (15 to 20 mg/kg over 20 min, if seizures continued, phenobarbitone (10 mg/kg) was intravenously administered over 20 min, if seizure recurred patients were labelled as refractory of intravenous diazepam (0.2 to 0.3 mg/kg) which was repeated after 5 if seizure reoccurred, this was followed by phenytoin (15 to 20 mg/kg over 20 min, if seizures continued, phenobarbitone (10 mg/kg) was intravenously administered over 20 min, if seizure recurred patients were labelled as refractory. Indirectness: No indirectness Further details: 1. Dose: Define (1 mg/kg). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (n=10) Intervention 2: Drug - Midazolam. dose/quantity, brand name, extra details. Duration Immediately. Concurrent medication/care: Previously: intravenous diazepam (0.2 to 0.3 mg/kg) which was repeated after 5 if seizure reoccurred, this was followed by phenytoin (15 to 20 mg/kg over 20 min, if seizures continued, phenobarbitone (10 mg/kg) was intravenously administered over 20 min, if seizure recurred patients were labelled as refractory of intravenous diazepam (0.2 to 0.3 mg/kg) which was repeated after 5 if seizure reoccurred, this was followed by phenytoin (15 to 20 mg/kg over 20 min, if seizures continued, phenobarbitone (10 mg/kg) was intravenously administered over 20 min, if seizure recurred patients were labelled as refractory. Indirectness: No indirectness Further details: 1. Dose: Define (0.15 mg/kg). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: High risk of bias 4. Route of administration:

Study	Fallah 2007[55]
	intravenous 5. Study location: Rest of the world
Funding	Academic or government funding (Deputy for research of Shaheed Beheshti University of Medical Sciences and Health Services, Tehran, Iran)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LIGNOCAINE versus MIDAZOLAM Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome for Convulsive status epilepticus: Seizure cessation at Not stated; Group 1: 5/10, Group 2: 2/10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Lignocaine vs midazolam: symptomatic epilepsy 89% vs 90%, idiopathic epilepsy 29% vs 10%; Group 1 Number missing: Group 2 Number missing: Protocol outcome 2: Length of ICU stay - Actual outcome for Convulsive status epilepticus: Length of hospital stay at Not stated; Group 1: mean 4.6 Days (SD 3.4); n=10, Group 2: mean 3.4 Days (SD 5.7); n=10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Lignocaine vs midazolam: symptomatic epilepsy 89% vs 90%, idiopathic epilepsy 29% vs 10%; Group 1 Number missing: Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality (including SUDEP) ; Time to event seizure cessation; Seizure recurrence greater than or less than 24 hours after administration of monotherapy; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance); Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

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Study	Gujjar 2017[63]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Oman; Setting: ED
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	SE defined as a prolonged (<5 min) or recurrent generalised tonic-clonic seizure(s) with no regaining of consciousness between attacks, or partial seizures persisting for more than 10 min
Exclusion criteria	Known allergy to drugs used, requirement of surgery, haemodynamic compromise, serious arrythmia, pregnancy, heart failure, pulmonary oedema, in pre-terminal states or having pseudo seizures, subtle SE defined as altered mental status without overt convulsions, but ongoing epileptiform activity noted on EEG
Age, gender and ethnicity	Age - Mean (SD): 37.8 (18). Gender (M:F): 34/18. Ethnicity: Not stated
Further population details	1. Age: Adults
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Drug - Levetiracetam. Intravenous levetiracetam: 30 mg/kg over 30 min . Duration Immediately. Concurrent medication/care: Not stated, previously lorazepam (4 mg) or diazepam (5-10 mg) over 2 min . Indirectness: No indirectness Further details: 1. Dose: Define (30 mg/kg). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: Low risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (n=30) Intervention 2: Drug - Phenytoin. Intravenous phenytoin: 20 mg/kg at a maximum rate of 50 mg/min

Study	Gujjar 2017[63]
	. Duration Immediately. Concurrent medication/care: Not stated, previously lorazepam (4 mg) or diazepam (5-10 mg) over 2 min. Indirectness: No indirectness Further details: 1. Dose: Define (20 mg/kg). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: Low risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world
Funding	Academic or government funding (Dean's Fund, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LEVETIRACETAM versus PHENYTOIN

Protocol outcome 1: Mortality (including SUDEP)
- Actual outcome for Convulsive status epilepticus: Mortality at 24 hours; Group 1: 2/22, Group 2: 3/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Levetiracetam vs phenytoin: epilepsy- 50% vs 60%, remote symptoms- 36.4% vs 26.7%, acute symptoms- 13.6% vs 16.7%; Group 1 Number missing: Group 2 Number missing:

Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive))
- Actual outcome for Convulsive status epilepticus: Seizure cessation within 24 hours at 24 hours; Group 1: 18/22, Group 2: 21/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Levetiracetam vs phenytoin: epilepsy- 50% vs 60%, remote symptoms- 36.4% vs 26.7%, acute symptoms- 13.6% vs 16.7%; Group 1 Number missing: Group 2 Number missing:

Protocol outcome 3: Quality of life
- Actual outcome for Convulsive status epilepticus: Good outcome at discharge: mRS score at Discharge; Group 1: 12/22, Group 2: 12/30
Risk of bias: All domain - --, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Levetiracetam vs phenytoin: epilepsy- 50% vs 60%, remote symptoms- 36.4% vs 26.7%, acute symptoms- 13.6% vs 16.7%; Group 1 Number missing: Group 2 Number missing:

Protocol outcome 4: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance)
- Actual outcome for Convulsive status epilepticus: Hypotension at 24 hours; Group 1: 0/22, Group 2: 2/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Levetiracetam vs phenytoin: epilepsy- 50% vs 60%, remote symptoms- 36.4% vs

Study	Gujjar 2017[63]
26.7%, acute symptoms- 13.6% vs 16.7%; Group 1 Number missing: Group 2 Number missing:	
Protocol outcomes not reported by the study	Time to event seizure cessation; Seizure recurrence greater than or less than 24 hours after administration of monotherapy; Time to seizure recurrence after administration of monotherapy; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

1

Study (subsidiary papers)	Lyttle 2019[107] (Lyttle 2017[106])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=286)
Countries and setting	Conducted in United Kingdom; Setting: Emergency departments
Line of therapy	2nd line
Duration of study	Intervention + follow up: 14 days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 6 months to <18 years who present with generalised tonic-clonic, generalised clonic, or focal clonic CSE that requires second-line treatment, provided that first-line treatment has been administered according to APLS guidelines [5] or the child's personalised rescue care plan. If patients are given more than two doses of benzodiazepines (for example, in the community and then the ED), or fewer than two doses (for example, due to previous benzodiazepine sensitivity), or where the personalised care plan includes rectal paraldehyde as first-line treatment, then they are still eligible. Children receiving oral phenytoin or levetiracetam as maintenance therapy are eligible.
Exclusion criteria	Children are excluded if they: 1) present with absence, myoclonic, or non-convulsive status epilepticus, or infantile spasms; 2) are known or suspected to be pregnant; 3) have a known contraindication or allergy to levetiracetam or phenytoin;

Study (subsidiary papers)	Lyttle 2019[107] (Lyttle 2017[106])
	4) have known established renal failure; 5)have been given a second-line antiepileptic drug during this episode of CSE prior to eligibility assessment; or 6) are known to have previously been treated in the EcLiPSE study.
Age, gender and ethnicity	Age - Median (IQR): LEV - 2.7 years (1.3 to 5.9), PHENY - 2.7 (1.6 to 5.6). Gender (M:F): 147 male, 139 female. Ethnicity: Not stated.
Further population details	1. Age: Children
Indirectness of population	No indirectness
Interventions	(n=212) Intervention 1: Drug - Levetiracetam. Levetiracetam - Levetiracetam was administered over 5 min in a dose of 40 mg/kg (maximum dose 2·5 g). Duration 5 min. Concurrent medication/care: Clinicians treated subsequent ongoing convulsive status epilepticus according to the APLS algorithm. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location: (n=192) Intervention 2: Drug - Phenytoin. Phenytoin - administered over a minimum of 20 min in a dose of 20 mg/kg (maximum dose 2 g and with a maximum infusion rate of 1 mg/kg per min). Duration 20 min. Concurrent medication/care: Clinicians treated subsequent ongoing convulsive status epilepticus according to the APLS algorithm. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location:
Funding	Academic or government funding (National Institute for Health Research Health Technology Assessment programme.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LEVETIRACETAM versus PHENYTOIN

Protocol outcome 1: Mortality (including SUDEP)
- Actual outcome for Convulsive status epilepticus: Mortality at 14 days; Group 1: 1/152, Group 2: 1/134
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Seizure type (generalised tonic-clonic [107/105], generalised clonic [12/7], focal clonic [33/22]), gender, age (2.7 years); Group 1 Number missing: 60, Reason: 51 did not require 2nd line treatment, 1 consent incompletely documented, 8 declined consent; Group 2 Number missing: 58, Reason: 42 did not require 2nd line treatment, 5 consent incompletely documented, 11 declined consent

Study (subsidiary papers)	Lyttle 2019[107] (Lyttle 2017[106])
Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome for Convulsive status epilepticus: Median time from randomisation to seizure cessation at N/A; levetiracetam (n=152) - 35 min Phenytoin (n=134) - 45 min The unadjusted HR was 1·20 (95% CI 0·91–1·60; p=0·20) in favour of levetiracetam.; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Seizure type (generalised tonic-clonic [107/105], generalised clonic [12/7], focal clonic [33/22]), gender, age (2.7 years); Group 1 Number missing: 60/212 = 28%, Reason: 51 did not require 2nd line treatment, 1 consent incompletely documented, 8 declined consent; Group 2 Number missing: 58/192 = 30%, Reason: 42 did not require 2nd line treatment, 5 consent incompletely documented, 11 declined consent Protocol outcome 3: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) - Actual outcome for Convulsive status epilepticus: Hypotension at N/A; Group 1: 2/132, Group 2: 3/130 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Seizure type (generalised tonic-clonic [107/105], generalised clonic [12/7], focal clonic [33/22]), gender, age (2.7 years); Group 1 Number missing: 60, Reason: 51 did not require 2nd line treatment, 1 consent incompletely documented, 8 declined consent; Group 2 Number missing: 58, Reason: 42 did not require 2nd line treatment, 5 consent incompletely documented, 11 declined consent - Actual outcome for Convulsive status epilepticus: Confusion at N/A; Group 1: 1/132, Group 2: 0/130 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Seizure type (generalised tonic-clonic [107/105], generalised clonic [12/7], focal clonic [33/22]), gender, age (2.7 years); Group 1 Number missing: 60, Reason: 51 did not require 2nd line treatment, 1 consent incompletely documented, 8 declined consent; Group 2 Number missing: 58, Reason: 42 did not require 2nd line treatment, 5 consent incompletely documented, 11 declined consent - Actual outcome for Convulsive status epilepticus: Admission to critical care at N/A; Group 1: 97/152, Group 2: 72/134 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Seizure type (generalised tonic-clonic [107/105], generalised clonic [12/7], focal clonic [33/22]), gender, age (2.7 years); Group 1 Number missing: 60, Reason: 51 did not require 2nd line treatment, 1 consent incompletely documented, 8 declined consent; Group 2 Number missing: 58, Reason: 42 did not require 2nd line treatment, 5 consent incompletely documented, 11 declined consent	
Protocol outcomes not reported by the study	Time to event seizure cessation; Seizure recurrence greater than or less than 24 hours after administration of monotherapy; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two

Study (subsidiary papers)	Lyttle 2019[107] (Lyttle 2017[106])
	groups; Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

1

Study	Handral 2020[65]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=116)
Countries and setting	Conducted in India; Setting: emergency department in a tertiary care hospital
Line of therapy	2nd line
Duration of study	Intervention + follow up: 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	children who presented with SE in the age group from 1 month to 18 years and did not respond to two doses of lorazepam 0.1 mg/kg/dose.
Exclusion criteria	patients who were previously on oral phenytoin and LEV for seizure prophylaxis, with known allergy to above drugs, myoclonic and absence seizures, seizures due to hypoglycaemia (<50 mg/dL), hypocalcaemia (serum ionized calcium: < 4.5 mg/dL), and acute hyponatremia (serum sodium: < 120 meq/dL).
Age, gender and ethnicity	Age - Mean (SD): LEV: 3.09+2.98; FHP: 3.77+3.79. Gender (M:F): 68/48. Ethnicity: not stated
Further population details	1. Age: Children (LEV: 3.09+2.98; FHP: 3.77+3.79).
Indirectness of population	No indirectness
Interventions	(n=58) Intervention 1: Drug - Levetiracetam. intravenous LEV 30 mg/kg over 10 min. Duration 10 minutes. Concurrent medication/care: two previous doses of lorazepam 0.1 mg/kg/dose. Indirectness: No indirectness Further details: 1. Dose: Define (30 mg/kg over 10 min). 2. Non convulsive by type: Not stated / Unclear (generalized convulsive status epilepticus). 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (India).

Study	Handral 2020[65]
	(n=58) Intervention 2: Drug - Fosphenytoin. FHP infusion 30 mg/kg over 20 min. Duration 20 minutes. Concurrent medication/care: two previous doses of lorazepam 0.1 mg/kg/dose. Indirectness: No indirectness Further details: 1. Dose: Define (30 mg/kg over 20 min). 2. Non convulsive by type: Not stated / Unclear (generalized convulsive status epilepticus). 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (India).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LEVETIRACETAM versus FOSPHENYTOIN Protocol outcome 1: Seizure recurrence greater than or less than 24 hours after administration of monotherapy at Define - Actual outcome for Convulsive status epilepticus: Recurrence of Seizures at up to 48h after administration of medication; Group 1: 10/58, Group 2: 13/58 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at Define - Actual outcome for Convulsive status epilepticus: Need for tracheal intubation at up to 48h after administration of medication; Group 1: 1/58, Group 2: 3/58 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Convulsive status epilepticus: Bradycardia at up to 48h after administration of medication; Group 1: 0/58, Group 2: 1/58 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Time to seizure cessation at 30 min - Actual outcome for Convulsive status epilepticus: Seizure cessation from 10 - 20 minutes at 10 - 20 minutes; Group 1: 53/58, Group 2: 54/58 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at Define; Time to seizure cessation, (5 minutes after drug administration, 10 mins, 30 mins, 60 mins, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) at Define; Time to event seizure

Study	Handral 2020[65]
	cessation at Define; Time to seizure recurrence after administration of monotherapy at Define; Quality of life at Define; Length of ICU stay at Define; Length of hospital stay at Define; mean Glasgow outcome scale (% difference in the means between the two groups at Define; Healthcare resource use at Define; Time to seizure cessation at 1 month; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

1

Study	Malamiri 2012[111]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Iran; Setting: 2 major university paediatric hospitals
Line of therapy	2nd line
Duration of study	Intervention + follow up: 24 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Enrolled children with aged 2 years and older presenting with convulsive status epilepticus or acute prolonged convulsive seizures.
Exclusion criteria	Excluded those with a history of adverse reactions to sodium valproate or similar drugs, a history of uncontrolled bleeding, thrombocytopenia, active hepatic disease, cardiac rhythm disturbances, orthostatic hypotension, or syncope and children who had received high doses of lamotrigine (more than 200 mg/day).
Age, gender and ethnicity	Age - Median (range): VALP -5 years (3-16), PHENO - 4 years (3-11). Gender (M:F): 37 boys, 23 girls. Ethnicity: not stated.
Further population details	1. Age: Children
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Drug - Valproate (sodium valproate / valproic acid). Sodium valproate - given at loading dose of 20mg/kg, diluted in 20ml saline, at a maximum rate of 5-6mg/kg per minute over 5-10 min via an infusion pump. Depakine sodium valproate was provided by a Sanofi company representative in Iran. The sodium

Study	Malamiri 2012[111]
	maintenance dose was continuous infusion pf 1mg/kg per hour, given 60 min after the bolus dose. Duration N/A. Concurrent medication/care: In each patient, intravenous maintenance doses were continued until the patient was able to take oral medications. All patients were monitored. Following discharge, all patients were referred to the child neurology clinic for follow-up. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location: (n=30) Intervention 2: Drug - Phenobarbital. Phenobarbital - given at a loading dose of 20mg/kg via an infusion pump at a rate not faster than 60-100mg/min. Duration N/A. Concurrent medication/care: In each patient, intravenous maintenance doses were continued until the patient was able to take oral medications. All patients were monitored. Following discharge, all patients were referred to the child neurology clinic for follow-up. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location:
Funding	Equipment / drugs provided by industry (Special thanks to Dr. Sadjad Bakhtiar and the Sanofi company for providing the Depakine used in this study.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALPROATE (SODIUM VALPROATE / VALPROIC ACID) versus PHENOBARBITAL

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive))
- Actual outcome for Convulsive status epilepticus: Seizure control in 20 min at 20 min; Group 1: 27/30, Group 2: 23/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: VAL/PHENO; symptomatic epilepsy - 21/13, idiopathic epilepsy - 4/7, febrile - 5/10; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Seizure recurrence greater than or less than 24 hours after administration of monotherapy
- Actual outcome for Convulsive status epilepticus: Seizure recurrence in 24 hours at 24 hours; Group 1: 4/27, Group 2: 12/23
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: VAL/PHENO; symptomatic epilepsy - 21/13, idiopathic epilepsy - 4/7, febrile - 5/10; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Study	Malamiri 2012[111]
Protocol outcome 3: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) - Actual outcome for Convulsive status epilepticus: Significant hypotension at N/A; Group 1: 1/30, Group 2: 0/30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: VAL/PHENO; symptomatic epilepsy - 21/13, idiopathic epilepsy - 4/7, febrile - 5/10; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome for Convulsive status epilepticus: Respiratory depression at N/A; Group 1: 0/30, Group 2: 1/30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: VAL/PHENO; symptomatic epilepsy - 21/13, idiopathic epilepsy - 4/7, febrile - 5/10; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Mortality (including SUDEP) ; Time to event seizure cessation; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

1

Study	Masapu 2018[113]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=23)
Countries and setting	Conducted in India
Line of therapy	2nd line
Duration of study	Intervention time: 15 min
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients (16–60 years) with RSE of any aetiology, unresponsive to the first-line IV lorazepam (0.1 mg/kg) and any two of the second-line IV anti-epileptic drugs (phenytoin [15 mg/kg], valproate [20–25 mg/kg], and levetiracetam [30 mg/kg]) were included in the study.

Study	Masapu 2018[113]
Exclusion criteria	Patients with known allergy to the study drug, history of coronary artery disease, documented clinical or two-dimensional-echo cardiac evidence of the left ventricular dysfunction and those in hypotension were excluded from the study.
Age, gender and ethnicity	Age - Mean (range): propofol 49 (30 to 65), Midazolam 45 (26.75 to 48.5). Gender (M:F): 18 male, 5 female. Ethnicity: Not stated.
Further population details	1. Age:
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Drug - Other. Propofol - In the propofol group, TCI was started at a Cp of 1.0 µg/ml and escalated based on seizure response [Figure 1a]. If seizures recurred during propofol infusion, 20 mg IV bolus of propofol was administered. If the seizures recurred more than three times in 15 min, or the seizures were not controlled for 15 min, then the dose was escalated by 0.5 µg/ml. The Cp of propofol required for successful seizure control was recorded. If seizures were not controlled even at Cp 2.5 µg/ml, the SE was considered super refractory and study drug treatment failure was recorded. Thereafter, the study drug infusion was terminated and thiopentone administered as a 3 mg/kg bolus followed by a continuous infusion at a rate of 3–5 mg/kg/hour. Duration N/A. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location: (n=12) Intervention 2: Drug - Midazolam. Midazolam - In midazolam group, the study drug was administered as a bolus of 0.05 mg/kg followed by an infusion as per the study protocol [Figure 1b]. In case seizures recurring with this dose, 0.05 mg/kg IV bolus was administered. If the seizures recurred >3 times in 15 min, or the seizures were not controlled for 15 min, the dose was escalated to next higher level as shown in Figure 1. If the seizures are not controlled at an infusion dose of 0.4 mg/kg/h, the SE was considered super-refractory, and treatment failure of the study drug was considered. Thereafter, thiopentone infusion was initiated with a bolus of 3 mg/kg followed by a continuous infusion at a rate of 3–5 mg/kg/hour Duration N/A. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location:
Funding	No funding

Study	Masapu 2018[113]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPOFOL versus MIDAZOLAM Protocol outcome 1: Mortality (including SUDEP) - Actual outcome: Mortality at N/A; Group 1: 8/11, Group 2: 7/12 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: type of seizure: Generalized tonic-clonic/complex partial seizures (%) MID-25/66.7, PRO - 45.5/55.5; Group 1 Number missing: 1, Reason: One patient lost to follow up due to discharge against medical advice; Group 2 Number missing: 0 Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome: Successful seizure control at N/A; Group 1: 5/11, Group 2: 3/12 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: type of seizure: Generalized tonic-clonic/complex partial seizures (%) MID-25/66.7, PRO - 45.5/55.5; Group 1 Number missing: 1, Reason: One patient lost to follow up due to discharge against medical advice; Group 2 Number missing: 0 Protocol outcome 3: Time to event seizure cessation - Actual outcome: Median time taken for immediate control of seizures in min (range) at N/A; Median (range) Propofol - 15 (10-20) Midazolam - 20 (15-27.5); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: type of seizure: Generalized tonic-clonic/complex partial seizures (%) MID-25/66.7, PRO - 45.5/55.5; Group 1 Number missing: 1, Reason: One patient lost to follow up due to discharge against medical advice; Group 2 Number missing: 0 Protocol outcome 4: Length of ICU stay - Actual outcome: Median duration of ICU stay in days at N/A; Median (range) Propofol - 11 (6-13.5) Midazolam - 15 (14.25-23); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: type of seizure: Generalized tonic-clonic/complex partial seizures (%) MID-25/66.7, PRO - 45.5/55.5; Group 1 Number missing: 1, Reason: One patient lost to follow up due to discharge against medical advice; Group 2 Number missing: 0 Protocol outcome 5: Length of hospital stay	

Study	Masapu 2018[113]
- Actual outcome: Median duration of hospital stay in days at N/A; Median (range) propofol - 11 (6-13.5) midazolam - 20.5 (15.75-43.25); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: type of seizure: Generalized tonic-clonic/complex partial seizures (%) MID-25/66.7, PRO - 45.5/55.5; Group 1 Number missing: 1, Reason: One patient lost to follow up due to discharge against medical advice; Group 2 Number missing: 0 Protocol outcome 6: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) - Actual outcome: Hypotension at N/A; Group 1: 3/11, Group 2: 1/12 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: type of seizure: Generalized tonic-clonic/complex partial seizures (%) MID-25/66.7, PRO - 45.5/55.5; Group 1 Number missing: 1, Reason: One patient lost to follow up due to discharge against medical advice; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Seizure recurrence greater than or less than 24 hours after administration of monotherapy; Time to seizure recurrence after administration of monotherapy; Quality of life; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

1

Study	Mehta 2007[120]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in India
Line of therapy	3rd line
Duration of study	Intervention + follow up: 6 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	Mehta 2007[120]
Inclusion criteria	Consecutive children, 5 months to 12 years of age, with refractory convulsive status epilepticus, admitted over a period of 1½ years to the Emergency and Neurology wards of the Advanced Paediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, were enrolled in the study.
Exclusion criteria	Neonates and infants up to 3 months of age as well as known or suspected cases of mitochondrial disorders were excluded.
Recruitment/selection of patients	Patients in whom seizures were not controlled after a bolus of diazepam (0.2 mg/kg) followed by phenytoin (20 mg/kg in normal saline infusion) and a repeat dose of phenytoin (5 to 10mg/kg in normal saline infusion) 10 min after the first dose were considered to have refractory status epilepticus.
Age, gender and ethnicity	Age - Mean (SD): valproate - 36.3months (32.8), diazepam - 44.5 months (42.8). Gender (M:F): 9 female, 31 male. Ethnicity: Not stated.
Further population details	1. Age: Children
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Drug - Valproate (sodium valproate / valproic acid). Valproate was given as an initial loading bolus of 30 mg/kg diluted 1:1 in normal saline from 2 to 5 min. If the status was not controlled within 10 min after the bolus dose, a repeat bolus dose of 10 mg/kg was given. This was followed by infusion at a rate of 5 mg/kg/hour, which was continued until a seizure-free period of 6 hours was reached and then reduced at a rate of 1 mg/kg/hr every 2 hours. After discontinuation of intravenous infusion, a maintenance dose of 10 mg/kg intravenous every 8 hours was continued until the child could take oral anticonvulsants. If seizures were not controlled within 30 min of giving intravenous sodium valproate, this was considered a failure of valproate therapy and diazepam was given as the next line of treatment, and if there was no response to the maximum dose of diazepam infusion (100 µg/kg/min) thiopental infusion was given. Duration N/A. Concurrent medication/care: Ventilation was started if the patient was unable to maintain adequate oxygenation on supplemental oxygen after intubation, had irregular breathing, or an episode of apnoea. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location: (n=20) Intervention 2: Drug - Diazepam. In the diazepam group, the infusion was started at a rate of 10 µg/kg/min and was increased every 5 min by 10 µg/kg/min

Study	Mehta 2007[120]
	until status was controlled or a maximum dose of 100 µg/kg/min was reached. The infusion was continued for at least 6 hours after control of the last seizure and then was gradually tapered at a rate of 10 µg/kg/min every 2 hours. If seizures were not controlled with the maximum dose of diazepam, it was considered a failure of diazepam therapy and thiopental was then used. Thiopental was given in a loading dose of 3 mg/kg followed by a continuous infusion of 0.2mg/kg/min until the seizures were controlled. Duration N/A. Concurrent medication/care: Ventilation was started if the patient was unable to maintain adequate oxygenation on supplemental oxygen after intubation, had irregular breathing, or an episode of apnoea. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALPROATE (SODIUM VALPROATE / VALPROIC ACID) versus DIAZEPAM

Protocol outcome 1: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive))
- Actual outcome: time interval for control of RSE after giving study drug (min) at N/A; Group 1: mean 8.8 (SD 7.4); n=20, Group 2: mean 26.6 (SD 26.7); n=20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: type of seizure VPA/DIAZ; Generalised tonic-clonic - 9/9, Focal with secondary generalization - 7/5, Simple partial - 3/5, Multifocal - 1/1; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Length of ICU stay
- Actual outcome: Admitted to paediatric ICU at N/A; Group 1: 11/20, Group 2: 19/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: type of seizure VPA/DIAZ; Generalised tonic-clonic - 9/9, Focal with secondary generalization - 7/5, Simple partial - 3/5, Multifocal - 1/1; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance)
- Actual outcome: Respiratory depression after drug administration at N/A; Group 1: 0/20, Group 2: 12/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Mehta 2007[120]
- Low; Indirectness of outcome: No indirectness; Baseline details: type of seizure VPA/DIAZ; Generalised tonic-clonic - 9/9, Focal with secondary generalization - 7/5, Simple partial - 3/5, Multifocal - 1/1; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Hypotension after drug administration at N/A; Group 1: 0/20, Group 2: 10/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: type of seizure VPA/DIAZ; Generalised tonic-clonic - 9/9, Focal with secondary generalization - 7/5, Simple partial - 3/5, Multifocal - 1/1; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Time to seizure cessation at 30 min - Actual outcome: RSE controlled within 30 min at 30 min; Group 1: 16/20, Group 2: 17/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: type of seizure VPA/DIAZ; Generalised tonic-clonic - 9/9, Focal with secondary generalization - 7/5, Simple partial - 3/5, Multifocal - 1/1; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality (including SUDEP) ; Time to event seizure cessation; Seizure recurrence greater than or less than 24 hours after administration of monotherapy; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

1

Study	Misra 2017[122]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=66)
Countries and setting	Conducted in India
Line of therapy	2nd line
Duration of study	Intervention + follow up: 24 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable

Study	Misra 2017[122]
Inclusion criteria	Consecutive patients with convulsive SE or subtle convulsive SE were recruited. Convulsive SE was defined as 2 or more convulsive seizures without full recovery or continuous convulsions lasting for more than 5 min.
Exclusion criteria	Patients with history of drug allergy, children (<18yrs), pregnancy, nonconvulsive SE, primary renal or hepatic failure, malignancy and those having received LCM or SVA were excluded.
Age, gender and ethnicity	Age - Median (range): LACO - 40 years (18-90), VALP - 40 years (18-85). Gender (M:F): 46 male, 20 female. Ethnicity: Not stated.
Further population details	1. Age: Adults
Extra comments	They received 4mg Lorazepam IV in 10ml saline in 2 to 4 min, which was repeated after 10 min if seizures were not controlled. Those who did not respond to second dose of Lorazepam were then randomised.
Indirectness of population	No indirectness
` +	(n=33) Intervention 1: Drug - Valproate (sodium valproate / valproic acid). Sodium valproate - sodium valproate 30mg/kg was administered intravenously at a rate of 100 mg/min. Duration N/A. Concurrent medication/care: If the seizures were not controlled in 10 min, the patients were treated with midazolam, levetiracetam, phenytoin, propofol or phenobarbitone at the discretion of treating physician. The patients were given supportive treatments such as antibiotics for infection, acyclovir for herpes simplex encephalitis artesunate for malaria, doxycycline or azithromycin for scrub typhus, and ampicillin for Leptospira. Fever was treated with cold sponging and paracetamol. Fluid, calories and electrolytes were provided. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location: (n=33) Intervention 2: Drug - Lacosamide. Lacosamide 400 mg intravenously was administered at a rate of 60 mg/min. Duration N/A. Concurrent medication/care: If the seizures were not controlled in 10 min, the patients were treated with midazolam, levetiracetam, phenytoin, propofol or phenobarbitone at the discretion of treating physician. The patients were given supportive treatments such as antibiotics for infection, acyclovir for herpes simplex encephalitis artesunate for malaria, doxycycline or azithromycin for scrub typhus, and ampicillin for Leptospira. Fever was treated with cold sponging and paracetamol. Fluid, calories and electrolytes were provided.] Indirectness: No indirectness

Study	Misra 2017[122]
	Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location:
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALPROATE (SODIUM VALPROATE / VALPROIC ACID) versus LACOSAMIDE

Protocol outcome 1: Mortality (including SUDEP)
- Actual outcome for Convulsive status epilepticus: Mortality at 57 days; Group 1: 12/33, Group 2: 10/33
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Type of seizure, generalised/subtle - LACO - 30/3, VALP - 32/1; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive))
- Actual outcome for Convulsive status epilepticus: Seizure cessation for 1 hour at 1 hour; Group 1: 23/33, Group 2: 21/33
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Type of seizure, generalised/subtle - LACO - 30/3, VALP - 32/1; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Time to event seizure cessation
- Actual outcome for Convulsive status epilepticus: The time for seizure cessation after starting study drug at N/A; Group 1: mean 7.52 (SD 2.64); n=33, Group 2: mean 8.13 (SD 2.34); n=33
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Type of seizure, generalised/subtle - LACO - 30/3, VALP - 32/1; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance)
- Actual outcome for Convulsive status epilepticus: Hypotension at N/A; Group 1: 0/33, Group 2: 1/33
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Type of seizure, generalised/subtle - LACO - 30/3, VALP - 32/1; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Time to seizure cessation at ≤ 24 hours

Study	Misra 2017[122]
- Actual outcome for Convulsive status epilepticus: 24 hour seizure freedom achieved at 24 hours; Group 1: 20/33, Group 2: 15/33 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Type of seizure, generalised/subtle - LACO - 30/3, VALP - 32/1; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Seizure recurrence greater than or less than 24 hours after administration of monotherapy; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at 1 month

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Study	Noureen 2019[144]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=600)
Countries and setting	Conducted in Pakistan; Setting: Department of Paediatric Neurology, The Children Hospital and Institute of Child Health Multan, Ab'dali Road, Chowk Fawara, Mohalla Qadirabad, Multan, Pakistan
Line of therapy	2nd line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female patients aged 1–14 years with generalized CSE who did not responding to two doses of diazepam (0.2 mg/kg to a maximum of 10 mg, administered 5 minutes apart) were included in the study at 5 minutes after the second dose of diazepam.
Exclusion criteria	Received anticonvulsant treatment other than benzodiazepine for the acute management of CSE. On assisted ventilation. Having CSE secondary to

	hypertensive encephalopathy, head injury, chronic kidney, or liver disease and electrolyte derangement (hypoglycaemia, hypercalcemia, hypo/hypernatremia, or hypomagnesemia). Presence of hypotension symptoms.
Recruitment/selection of patients	children presenting to an Emergency Department with CSE.
Age, gender and ethnicity	Age - Mean (SD): LEV: 3.52±0.24; PHT: 3.46±0.22. Gender (M:F): 406/84. Ethnicity:
Further population details	1. Age: Children (LEV: 3.52±0.24; PHT: 3.46±0.22).
Indirectness of population	No indirectness
Interventions	(n=300) Intervention 1: Drug - Levetiracetam. LEV was used in a dose of 40 mg/kg (maximum of 500 mg) infused over 15 minutes. The medication was diluted in normal saline. Supportive treatment (e.g., antipyretics and antibiotics) was provided simultaneously to both groups according to the hospital protocol. Duration 15 minutes for treatment. Concurrent medication/care: generalized CSE who did not respond to two doses of diazepam (0.2 mg/kg to a maximum of 10 mg, administered 5 minutes apart) were included in the study at 5 minutes after the second dose of diazepam. Further details: 1. Dose: Define (40mg/kg (maximum 500mg)). 2. Non convulsive by type: Not applicable (generalized convulsive status epilepticus). 3. Risk of bias of studies: High risk of bias (open label randomized controlled trial). 4. Route of administration: intravenous (IV administration). 5. Study location: Rest of the world (Pakistan). (n=300) Intervention 2: Drug - Phenytoin. PHT dose was 20 mg/kg (maximum of 250 mg) given over 30 minutes. The medication was diluted in normal saline. Supportive treatment (e.g., antipyretics and antibiotics) was provided simultaneously to both groups according to the hospital protocol. Duration 30 minutes. Concurrent medication/care: generalized CSE who did not respond to two doses of diazepam (0.2 mg/kg to a maximum of 10 mg, administered 5 minutes apart) were included in the study at 5 minutes after the second dose of diazepam. Indirectness: No indirectness Further details: 1. Dose: Define (PHT 20 mg/kg over 30 minutes). 2. Non convulsive by type: Not applicable (generalized convulsive status epilepticus). 3. Risk of bias of studies: High risk of bias (open labelled randomized controlled trial). 4. Route of administration: intravenous (IV administration). 5. Study location: Rest of the world (Pakistan).

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LEVETIRACETAM versus PHENYTOIN Protocol outcome 1: Time to seizure cessation, (5 minutes after drug administration, 10 mins, 30 mins, 60 mins, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome for Convulsive status epilepticus: Seizure cessation within 30 minutes at 30 minutes post administration of medication ; Group 1: 278/300, Group 2: 250/300 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - open labelled trial ; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) - Actual outcome for Convulsive status epilepticus: Cardiac depression at post administration of medication ; Group 1: 0/300, Group 2: 2/300 Risk of bias: All domain - ; Indirectness of outcome: No indirectness - Actual outcome for Convulsive status epilepticus: Respiratory depression at post administration of medication ; Group 1: 0/300, Group 2: 6/300 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - open labelled trial ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality (including SUDEP) ; Time to event seizure cessation; Seizure recurrence greater than or less than 24 hours after administration of monotherapy; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 1 month; Time to seizure cessation at 10 min; Time to seizure cessation at 30 min; Time to seizure cessation at 5 min; Time to seizure cessation at 60 min; Time to seizure cessation at ≤ 24 hours

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Study	**Singhi 2002[192]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in India
Line of therapy	3rd line
Duration of study	Not clear:

Study	Singhi 2002[192]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Children 2 months to 12 years of age in refractory convulsive status epilepticus who were consecutively admitted over a period of 11 1/2 years to the Emergency and Intensive Care Services of the Advance Paediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, were enrolled in the study.
Exclusion criteria	Neonates and children with primary cardiac or respiratory diseases or any other chronic illness were excluded.
Age, gender and ethnicity	Age - Mean (SD): MID - 40.6 months (44.3), DIAZ - 49.6 months (43.4). Gender (M:F): 31 male, 9 female. Ethnicity: Not stated.
Further population details	1. Age: Children
Extra comments	Patients whose seizures were not controlled after two bolus doses of diazepam (0.3 mg/kg) and phenytoin infusion (20 mg/kg in normal saline infusion over 20 min) followed by a repeat dose of benzodiazepine were considered to have refractory status epilepticus.
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Drug - Diazepam. Diazepam - In the diazepam group, the infusion was started at a rate of 0.01 mg/kg/min and was increased every 5 min at a rate of 0.01 mg/kg/min until the seizure was controlled or the maximum dose of 0.1 mg/kg/min was reached. Duration N/A. Concurrent medication/care: In both groups, infusion was continued for at least 6 hours after control of the last seizure and then was gradually tapered over 12 to 24 hours under clinical monitoring. If the seizure recurred after initial control, the infusion rate of the drug was increased until complete control of convulsive seizure without further recurrence or until the maximum dose limit was reached. If seizures were not controlled with the maximum dose of the study drug, thiopental (loading dose of 3 mg/kg followed by a continuous infusion of 0.2 mg/kg/min) was used. This was increased at a rate of 0.1 mg/kg/min every 10 min until seizures were controlled. The treatment protocols were fully adhered to. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location:

Study	Singhi 2002[192]
	(n=21) Intervention 2: Drug - Midazolam. Midazolam - were given a bolus of 0.2 mg/kg followed by a continuous intravenous infusion starting at 2.0 µg/kg until control of the seizure or up to a maximum of 10.0µg/kg/min. Duration N/A. Concurrent medication/care: In both groups, infusion was continued for at least 6 hours after control of the last seizure and then was gradually tapered over 12 to 24 hours under clinical monitoring. If the seizure recurred after initial control, the infusion rate of the drug was increased until complete control of convulsive seizure without further recurrence or until the maximum dose limit was reached. If seizures were not controlled with the maximum dose of the study drug, thiopental (loading dose of 3 mg/kg followed by a continuous infusion of 0.2mg/kg/min) was used. This was increased at a rate of 0.1 mg/kg/min every 10 min until seizures were controlled. The treatment protocols were fully adhered to. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus DIAZEPAM

Protocol outcome 1: Mortality (including SUDEP)
- Actual outcome: Mortality at N/A; Group 1: 8/21, Group 2: 2/19
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: seizure type, MID/DIAZ - simple partial with secondary generalisation - 14/16, simple partial - 2/2, generalised tonic clonic - 5/1; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive))
- Actual outcome: Time interval to initial control of RSE (min) at N/A; Group 1: mean 15.9 (SD 9.6); n=21, Group 2: mean 15.8 (SD 13); n=19
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: seizure type, MID/DIAZ - simple partial with secondary generalisation - 14/16, simple partial - 2/2, generalised tonic clonic - 5/1; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Time interval to final control of seizures (min) at N/A; Group 1: mean 135 (SD 222); n=21, Group 2: mean 54 (SD 105); n=19
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: seizure type, MID/DIAZ - simple partial with secondary generalisation - 14/16, simple partial - 2/2, generalised tonic clonic - 5/1; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Singhi 2002[192]
- Actual outcome: Controlled RSE for at least 6 hours at 6 hours; Group 1: 18/21, Group 2: 17/19 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: seizure type, MID/DIAZ - simple partial with secondary generalisation - 14/16, simple partial - 2/2, generalised tonic clonic - 5/1; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Seizure recurrence greater than or less than 24 hours after administration of monotherapy - Actual outcome: Seizure recurrence after stopping infusion at N/A; Group 1: 4/21, Group 2: 3/19 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: seizure type, MID/DIAZ - simple partial with secondary generalisation - 14/16, simple partial - 2/2, generalised tonic clonic - 5/1; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Seizure recurrence whilst on infusion at N/A; Group 1: 12/21, Group 2: 3/19 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: seizure type, MID/DIAZ - simple partial with secondary generalisation - 14/16, simple partial - 2/2, generalised tonic clonic - 5/1; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) - Actual outcome: Hypotension at N/A; Group 1: 8/21, Group 2: 9/19 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: seizure type, MID/DIAZ - simple partial with secondary generalisation - 14/16, simple partial - 2/2, generalised tonic clonic - 5/1; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Time to event seizure cessation; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

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Study	Su 2016[205]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=73)
Countries and setting	Conducted in China

Study	Su 2016[205]
Line of therapy	2nd line
Duration of study	Intervention + follow up: 3 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Convulsive status epilepticus
Subgroup analysis within study	Not applicable
Inclusion criteria	All adult patients (aged 18 years or older) with GCSE who were admitted to the emergency room or neurocritical care unit of the Xuanwu Hospital, Capital Medical University, initially received first-line treatment with diazepam (intravenous injection of 0.2 mg/kg, administered twice at a 10-min interval) according to hospital protocol. Patients who did not respond to first line treatment, and were eligible based on the study inclusion and exclusion criteria, were prospectively and consecutively enrolled into the trial. We applied an operational definition of SE as 5 min or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures, according to guidelines for the evaluation and management of SE.
Exclusion criteria	Exclusion criteria included (1) unstable vital signs, such as systolic blood pressure \90 mmHg, pulse \60 beats/min, or arterial blood oxygen saturation \90%; (2) liver dysfunction (alanine transaminase or total bilirubin more than twice the upper limit of normal); (3) neurologic emergency requiring immediate surgical intervention; (4) pregnant or breast-feeding; (5) hypersensitivity to study drugs.
Age, gender and ethnicity	Age - Mean (SD): 41.72 years (17.14). Gender (M:F): 38 male, 35 female. Ethnicity: Not stated
Further population details	1. Age: Adults
Extra comments	Those who had not responded to first-line anticonvulsants were enrolled in this trial and were randomized to receive either intravenous phenobarbital or valproate.
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: Drug - Phenobarbital. Intravenous phenobarbital - In the phenobarbital group, a loading dose of 20 mg/kg (an additional 5–10 mg/kg may be administered) began at a rate of 50 mg/min, followed by an intravenous dose of 100 mg every 6 h. Once the patient began to show hypopnea or hypotension, phenobarbital was stopped or stepped down for the time being. Duration N/A. Concurrent medication/care: The infusions were maintained for 24–48-hour and then gradually tapered until they were eventually replaced with oral AEDs (24–72

Study	Su 2016[205]
	hours). The blood–drug level was also tested. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location: (n=36) Intervention 2: Drug - Valproate (sodium valproate / valproic acid). Valproate In the valproate group, a loading dose of 30 mg/kg (an additional 15 mg/kg may be administered) began at a rate of 3 mg/kg/min, followed by a continuous infusion at a rate of 1–2 mg/kg/hour. Duration N/A. Concurrent medication/care: The infusions were maintained for 24–48 hours and then gradually tapered until they were eventually replaced with oral AEDs (24–72 hours). The blood–drug level was also tested. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location:
Funding	Academic or government funding (This study was supported by the National Key Department of Neurology funded by the Chinese Health and Family Planning Committee, and the National Key Department of Critical Care Medicine funded by the Chinese Health and Family Planning Committee.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENOBARBITAL versus VALPROATE (SODIUM VALPROATE / VALPROIC ACID)

Protocol outcome 1: Mortality (including SUDEP)
- Actual outcome: Mortality at 3 months at 3 months; Group 1: 6/37, Group 2: 11/36
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Aetiology, phenobarbital/valproate; epilepsy related - 14/9, virus encephalitis - 14/16, Cerebrovascular disease - 3/3, others - 6/8; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Seizure recurrence greater than or less than 24 hours after administration of monotherapy
- Actual outcome: Relapse rate of SE within 24 hours at 24 hours; Group 1: 2/30, Group 2: 5/16
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Aetiology, phenobarbital/valproate; epilepsy related - 14/9, virus encephalitis - 14/16, Cerebrovascular disease - 3/3, others - 6/8; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance)

Study	Su 2016[205]
- Actual outcome: Transient depressed respiration at N/A; Group 1: 6/37, Group 2: 0/36 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Aetiology, phenobarbital/valproate; epilepsy related - 14/9, virus encephalitis - 14/16, Cerebrovascular disease - 3/3, others - 6/8; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Hypotension at N/A; Group 1: 5/37, Group 2: 0/36 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Aetiology, phenobarbital/valproate; epilepsy related - 14/9, virus encephalitis - 14/16, Cerebrovascular disease - 3/3, others - 6/8; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Time to seizure cessation, (5 min after drug administration, 10 min, 30 min, 60 min, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)): Time to event seizure cessation; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Healthcare resource use; Time to seizure cessation at 1 month; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at 10 min; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 5 min; Time to seizure cessation at ≤ 24 hours

1

Study	Vignesh 2020[233]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=110)
Countries and setting	Conducted in India; Setting: Paediatric critical care division in a tertiary care institute from June, 2016 to December, 2018.
Line of therapy	2nd line
Duration of study	Intervention + follow up::
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 3 month to 12 years with convulsive status epilepticus (clonic, tonic, tonic-clonic, and myoclonic, focal or generalized) were enrolled.

Study	Vignesh 2020[233]
Exclusion criteria	Children with either of the following conditions were excluded (i) non-convulsive status epilepticus, (ii) active or recent haemorrhage (less than one week) from any site, (iii) documented platelet count less than 50,000, or international normalized ratio more than two, (iv) head injury or neurosurgery in the past one month, (v) acute or chronic liver or kidney disease, (vi) suspected or known neurometabolic or mitochondrial disorders or structural malformations, (vii) known or suspected allergy to any of the study drugs, (viii) patient with epilepsy already on levetiracetam (more than 20 mg per kg per day) or valproate (more than 20 mg per kg per day) or phenytoin (more than 5 mg per kg per day) for more than one month, and (ix) patients who have received the appropriate dose of study drug(s) for the current episode of convulsive status epilepticus.
Age, gender and ethnicity	Age - Mean (SD): (months) LEV: 58(50); PHT: 44(43); VAL: 59(44). Gender (M:F): 58/44. Ethnicity: Not stated.
Further population details	1. Age: Children
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Drug - Levetiracetam. injection levetiracetam (Levesam, 5 mL per 500 mg, Abbott Ind. Ltd, India) was at a concentration of 5 mg/mL in 0.9% normal saline dilution in the syringe. Patients not responding to intravenous lorazepam received the study drug at the dose of 20 mg kg over 20 minutes as an intravenous infusion. Duration 20 minutes. Concurrent medication/care: lorazepam 0.1 mg/kg in the paediatric emergency room. Indirectness: No indirectness Further details: 1. Dose: Define (20 mg kg over 20 minutes). 2. Non convulsive by type: Not stated / Unclear (convulsive status epilepticus). 3. Risk of bias of studies: Low risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (India). (n=35) Intervention 2: Drug - Phenytoin. phenytoin sodium (Ciroton, 2 mL per 100 mg, Ciron Pharmaceuticals, India) was prepared at a concentration of 5 mg/mL in 0.9% normal saline dilution in the syringe. Patients not responding to intravenous lorazepam received the study drug at the dose of 20 mg kg over 20 minutes as an intravenous infusion. Duration 20 minutes. Concurrent medication/care: lorazepam 0.1 mg/kg in the paediatric emergency room. Indirectness: No indirectness Further details: 1. Dose: Define (20 mg kg over 20 minutes). 2. Non convulsive by type: Not stated / Unclear (convulsive status epilepticus). 3. Risk of bias of studies:

Study	Vignesh 2020[233]
	Low risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (India). (n=35) Intervention 3: Drug - Valproate (sodium valproate / valproic acid). injection sodium valproate (Valprol, 5 mL per 500 mg, Intas Pharmaceuticals, India) was prepared at a concentration of 5 mg/mL in 0.9% normal saline dilution in the syringe. Patients not responding to intravenous lorazepam received the study drug at the dose of 20 mg kg over 20 minutes as an intravenous infusion. Duration 20 minutes. Concurrent medication/care: lorazepam 0.1 mg/kg in the paediatric emergency room. Indirectness: No indirectness Further details: 1. Dose: Define (20 mg kg over 20 minutes). 2. Non convulsive by type: Not stated / Unclear (convulsive status epilepticus). 3. Risk of bias of studies: Low risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (India).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LEVETIRACETAM versus PHENYTOIN Protocol outcome 1: Mortality (including SUDEP) - Actual outcome for Convulsive status epilepticus: Mortality at after admission; Group 1: 0/32, Group 2: 0/35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Time to seizure cessation, (5 minutes after drug administration, 10 mins, 30 mins, 60 mins, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome for Convulsive status epilepticus: Time to control seizure (minutes) at after starting the study drug infusion; Group 1: mean 3.1 minutes (SD 1.3); n=32, Group 2: mean 3 minutes (SD 1.2); n=35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of ICU stay - Actual outcome for Convulsive status epilepticus: PICU stay (days) at after admission; Group 1: mean 6 days (SD 3.7); n=32, Group 2: mean 4 days (SD 2.4); n=35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	

Study	Vignesh 2020[233]
	Protocol outcome 4: Length of hospital stay - Actual outcome for Convulsive status epilepticus: Hospital stay (days) at after admission; Group 1: mean 7 days (SD 7.4); n=32, Group 2: mean 6.1 days (SD 4.1); n=35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Time to seizure cessation at 30 min - Actual outcome for Convulsive status epilepticus: seizure cessation (15 minutes after drug administration) at 35 minutes after starting the study drug infusion; Group 1: 30/32, Group 2: 31/35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LEVETIRACETAM versus VALPROATE (SODIUM VALPROATE / VALPROIC ACID) Protocol outcome 1: Mortality (including SUDEP) - Actual outcome for Convulsive status epilepticus: Mortality at after admission; Group 1: 0/32, Group 2: 1/35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Time to seizure cessation, (5 minutes after drug administration, 10 mins, 30 mins, 60 mins, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome for Convulsive status epilepticus: Time to control seizure (minutes) at after starting the study drug infusion; Group 1: mean 3.1 minutes (SD 1.3); n=32, Group 2: mean 3.2 minutes (SD 1.4); n=35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of ICU stay - Actual outcome for Convulsive status epilepticus: PICU stay (days) at after admission; Group 1: mean 6 days (SD 3.7); n=32, Group 2: mean 10 days (SD 4.5); n=35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Vignesh 2020[233]
	Protocol outcome 4: Length of hospital stay - Actual outcome for Convulsive status epilepticus: Hospital stay (days) at after admission; Group 1: mean 7 days (SD 7.4); n=32, Group 2: mean 5.5 days (SD 5.4); n=35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Time to seizure cessation at 30 min - Actual outcome for Convulsive status epilepticus: seizure cessation (15 minutes after drug administration) at 35 minutes after starting the study drug infusion; Group 1: 30/32, Group 2: 29/35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENYTOIN versus VALPROATE (SODIUM VALPROATE / VALPROIC ACID) Protocol outcome 1: Mortality (including SUDEP) - Actual outcome for Convulsive status epilepticus: Mortality at after admission; Group 1: 0/35, Group 2: 1/35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Time to seizure cessation, (5 minutes after drug administration, 10 mins, 30 mins, 60 mins, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)) - Actual outcome for Convulsive status epilepticus: Time to control seizure (minutes) at after starting the study drug infusion; Group 1: mean 3 minutes (SD 1.2); n=35, Group 2: mean 3.2 minutes (SD 1.4); n=35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of ICU stay - Actual outcome for Convulsive status epilepticus: PICU stay (days) at after admission; Group 1: mean 4 days (SD 2.4); n=35, Group 2: mean 10 days (SD 4.5); n=35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Vignesh 2020[233]
Protocol outcome 4: Length of hospital stay - Actual outcome for Convulsive status epilepticus: Hospital stay (days) at after admission; Group 1: mean 6.1 days (SD 4.1); n=35, Group 2: mean 5.5 days (SD 5.4); n=35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Time to seizure cessation at 30 min - Actual outcome for Convulsive status epilepticus: seizure cessation (15 minutes after drug administration) at 35 minutes after starting the study drug infusion; Group 1: 31/35, Group 2: 29/35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Time to event seizure cessation; Seizure recurrence greater than or less than 24 hours after administration of monotherapy; Time to seizure recurrence after administration of monotherapy; Quality of life; mean Glasgow outcome scale (% difference in the means between the two groups; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance); Healthcare resource use; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 1 month; Time to seizure cessation at 10 min; Time to seizure cessation at 5 min; Time to seizure cessation at 60 min; Time to seizure cessation at ≤ 24 hours

1

2

Study	Wani 2019[238]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=104)
Countries and setting	Conducted in India
Line of therapy	2nd line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Study	Wani 2019[238]
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Children in the age group of 1 month to 12 years presenting with status epilepticus.
Exclusion criteria	Children already on antiepileptic medication, having head injury, very sick children with shock or impending respiratory failure and renal failure, and children hypersensitive to phenytoin or levetiracetam were excluded
Age, gender and ethnicity	Age - Mean (SD): LEV:3.39 ± 3.32; PHT: 4.80 ± 4.11. Gender (M:F): 66/38. Ethnicity: Not stated.
Further population details	1. Age: Children
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: Drug - Levetiracetam. Children in this group 1 were given levetiracetam at a dose of 40 mg/kg diluted in 50 mL of normal saline over 10 min followed by a maintenance dose of 20 mg/kg/day to be given in two divided doses 12 h after initial dose. If seizures recurred after the first loading of the drug, a further additional dose of 10 mg/kg of the same drug was given. If seizures still recurred, the patients were loaded with valproate with a dose of 20 mg/kg dissolved in 50 mL of normal saline over 10 min and further a maintenance dose of 20 mg/kg in two divided dose was given. Duration Until seizure control established. Concurrent medication/care: Children who came with active seizures were given midazolam at a dose of 0.1 mg/kg slowly. Indirectness: No indirectness Further details: 1. Dose: Define (40 mg/kg diluted in 50 mL of normal saline over 10 min followed by a maintenance dose of 20 mg/kg/day to be given in two divided doses 12 h after initial dose). 2. Non convulsive by type: Not stated / Unclear 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (India). (n=52) Intervention 2: Drug - Phenytoin. Children in the Phenytoin group were given IV phenytoin as 20 mg/kg diluted in normal saline over 20 min. If seizures recurred after the first loading of the drug, a further additional dose of 10 mg/kg of the same drug was given. If seizures still recurred, the patients were loaded with valproate with a dose of 20 mg/kg dissolved in 50 mL of normal saline over 10 min and further a maintenance dose of 20 mg/kg in two divided dose was given. Duration Until seizure control established. Concurrent medication/care: Children who came with

Study	Wani 2019[238]
	active seizures were given midazolam at a dose of 0.1 mg/kg slowly. Indirectness: No indirectness Further details: 1. Dose: Define (20 mg/kg diluted in normal saline over 20 min). 2. Non convulsive by type: Not stated / Unclear (69 - 78% generalized seizures; 17% focal seizures; 3-13.5% complex partial seizures). 3. Risk of bias of studies: High risk of bias 4. Route of administration: intravenous 5. Study location: Rest of the world (India).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LEVETIRACETAM versus PHENYTOIN Protocol outcome 1: Seizure recurrence greater than or less than 24 hours after administration of monotherapy - Actual outcome for Convulsive status epilepticus: Seizure recurrence at 24 hours post administration of medication; Group 1: 2/52, Group 2: 18/52 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Time to seizure cessation at 5 min - Actual outcome for Convulsive status epilepticus: Cessation of SE within 5 minutes at <5 minutes after administration of medication ; Group 1: 34/52, Group 2: 36/52 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Convulsive status epilepticus: Cessation of SE 5 - 20 minutes at 5-20 minutes after administration of medication ; Group 1: 17/52, Group 2: 15/52 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Convulsive status epilepticus: Cessation of SE from 20 - 40 minutes at 20-40 minutes after administration of medication ; Group 1: 1/52, Group 2: 1/52 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality (including SUDEP) ; Time to seizure cessation, (5 minutes after drug administration, 10 mins, 30 mins, 60 mins, less than or equal to 24 hours (convulsive), up to 1 month (non-convulsive)): Time to event seizure cessation; Time to seizure recurrence after administration of monotherapy; Quality of life; Length of ICU stay; Length of hospital stay; mean Glasgow outcome scale (% difference in the means between the two groups; Adverse events (respiratory

Study	Wani 2019[238]
	depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance); Healthcare resource use ; Time to seizure cessation at ≥ 24 hours; Time to seizure cessation at 1 month; Time to seizure cessation at 10 min; Time to seizure cessation at 30 min; Time to seizure cessation at 60 min; Time to seizure cessation at ≤ 24 hours

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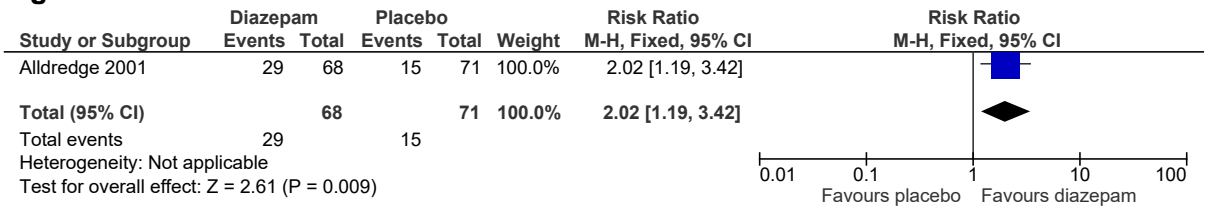
Appendix E: Forest plots

E.1 Monotherapy

E.1.1 Diazepam vs placebo

Figure 3: Termination of SE at time of arrival at ED



E.1.2 Diazepam vs drug (lorazepam or midazolam)

Figure 4: Mortality

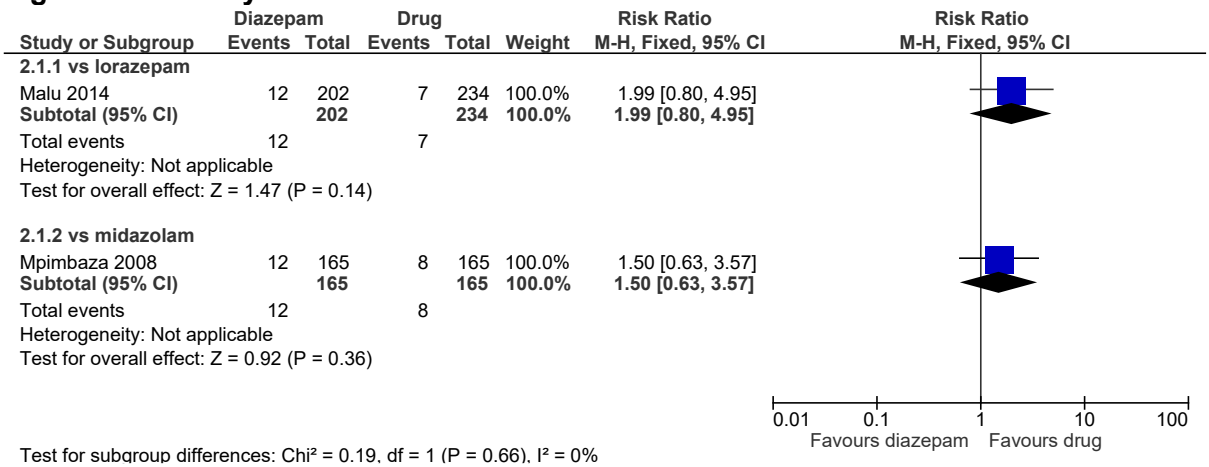


Figure 5: Termination of SE at time of arrival at ED

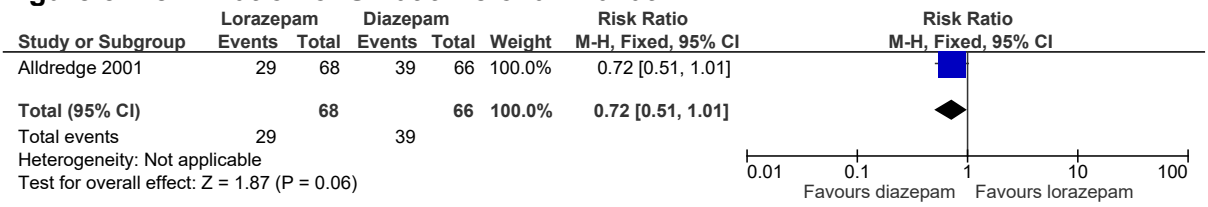


Figure 6: Termination of SE within 5 minutes

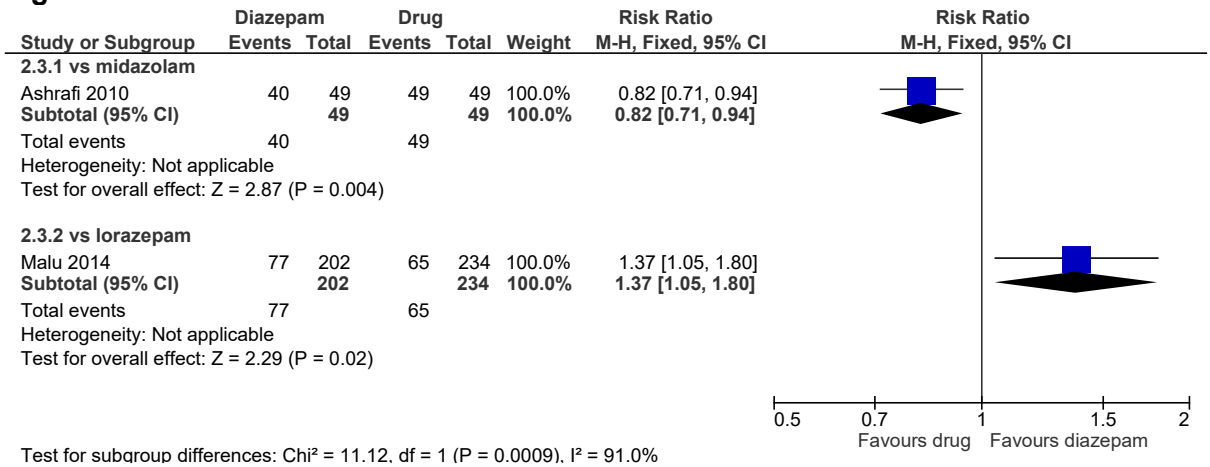


Figure 7: Termination of seizure within 10 min

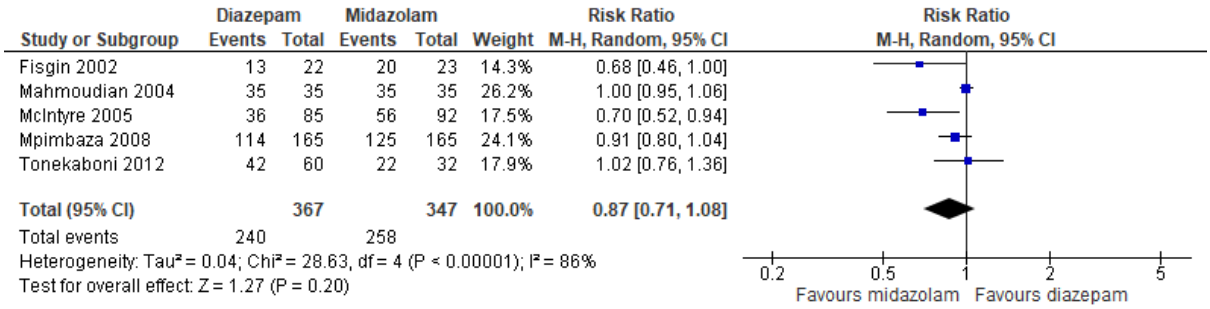


Figure 8: Termination of seizure within 10 min

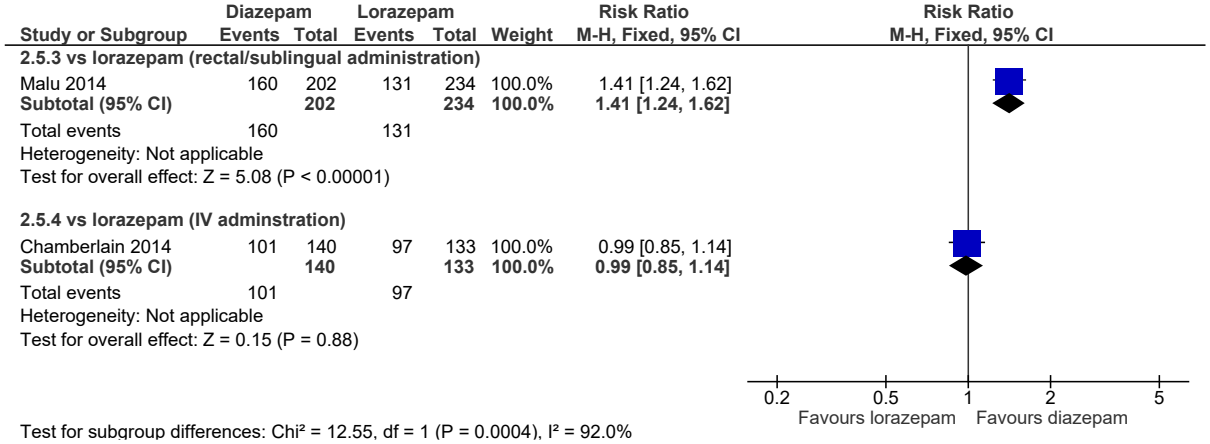


Figure 9: Termination of seizure within 20 min

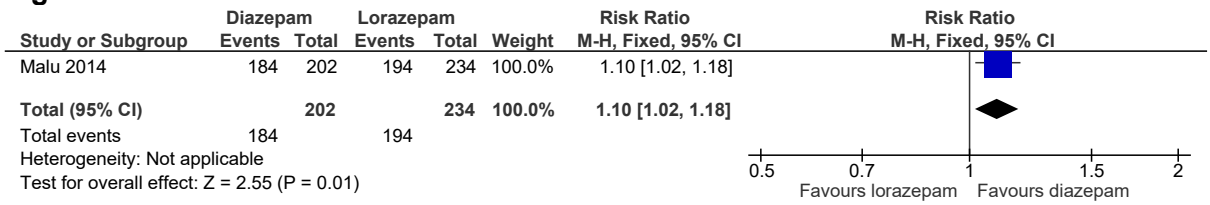


Figure 10: Time to clinical seizure cessation

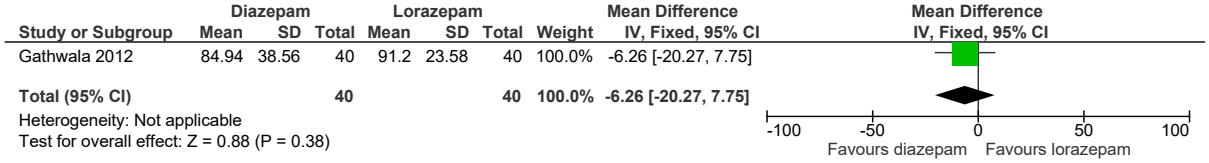


Figure 11: Time to cessation after drug administration

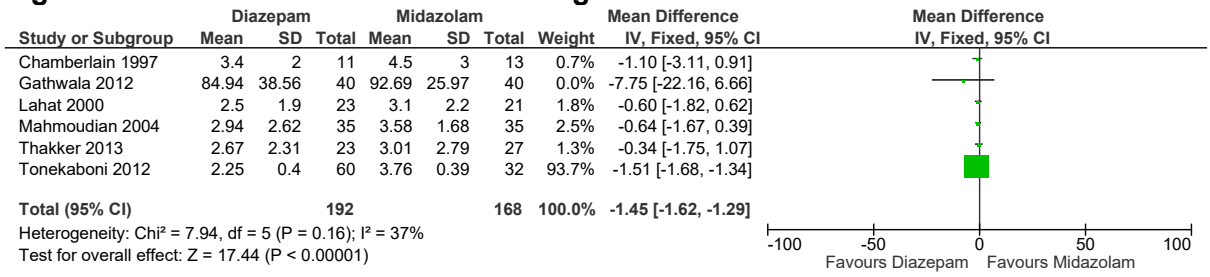


Figure 12: Seizure recurrence within 24 hours (UK)

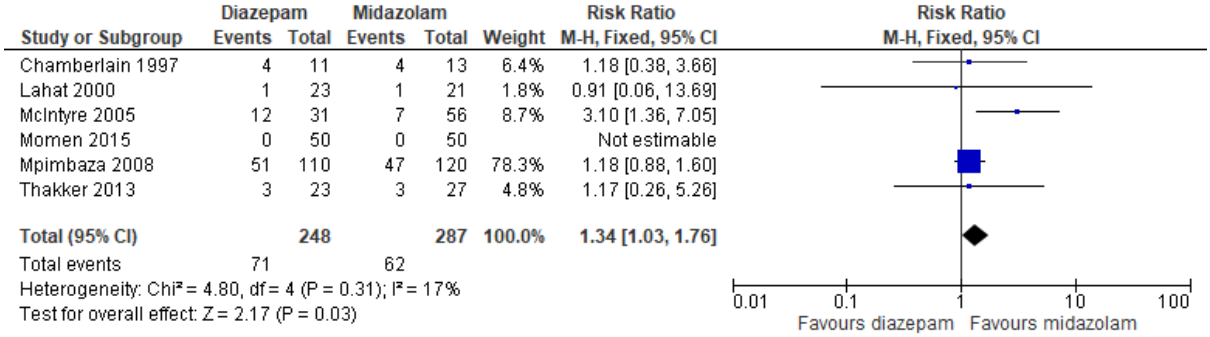


Figure 13: Seizure recurrence within 24 hours

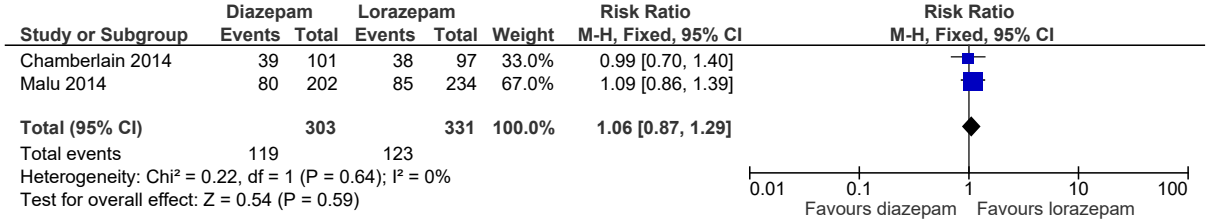


Figure 14: Adverse events, Respiratory depression

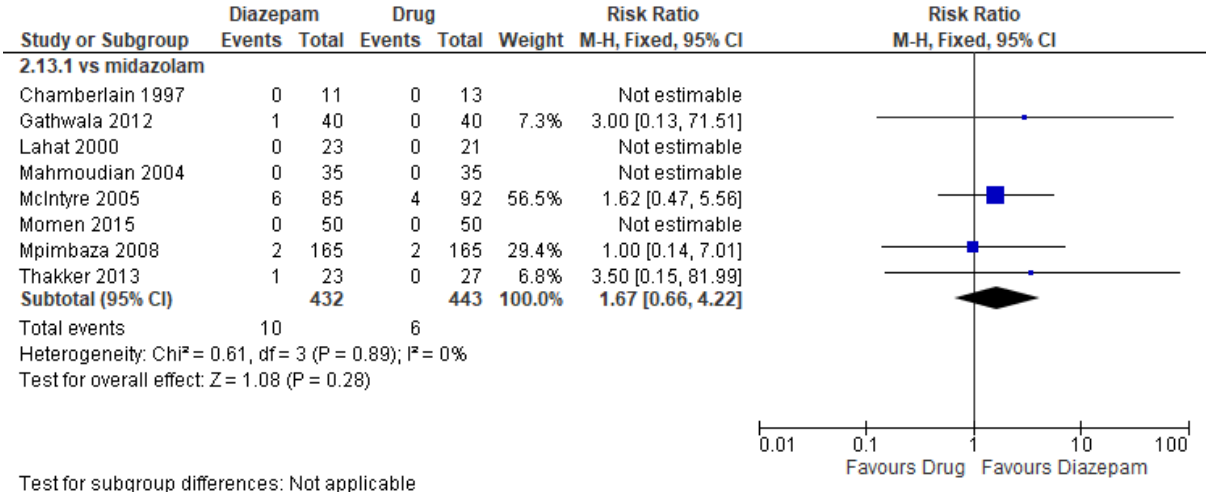
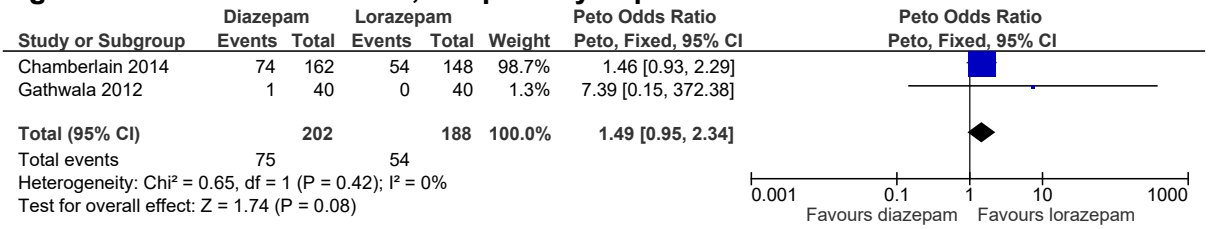
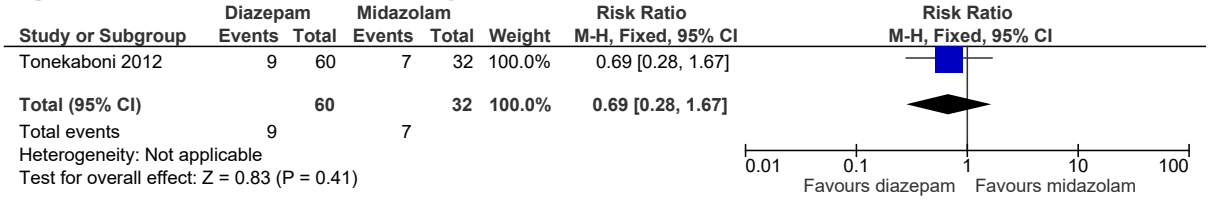


Figure 15: Adverse events, Respiratory depression



1

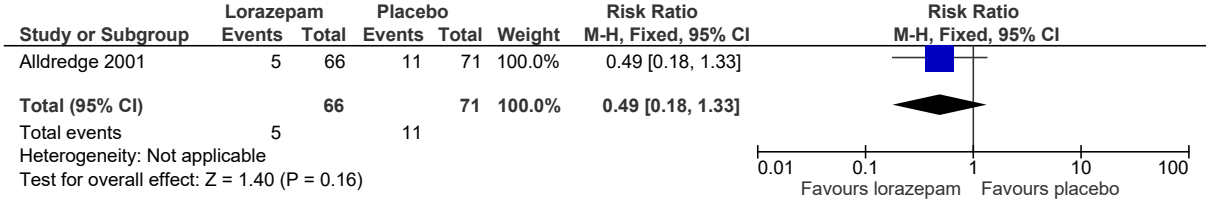
Figure 16: Adverse events, hypotension



2

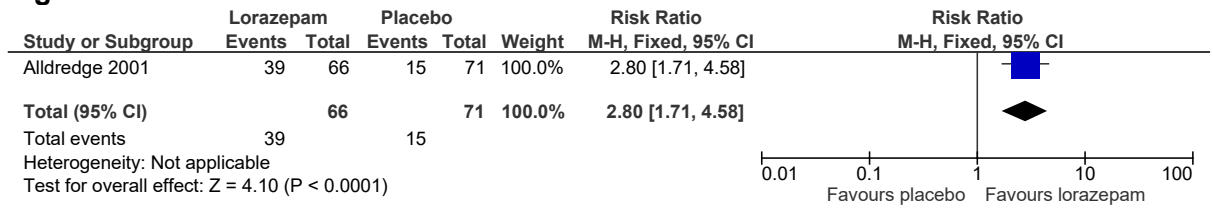
3 E.1.3 Lorazepam vs placebo

Figure 17: Mortality



4

Figure 18: Termination of SE at time of arrival at ED



E.1.4 Lorazepam vs drug

Figure 19: Mortality

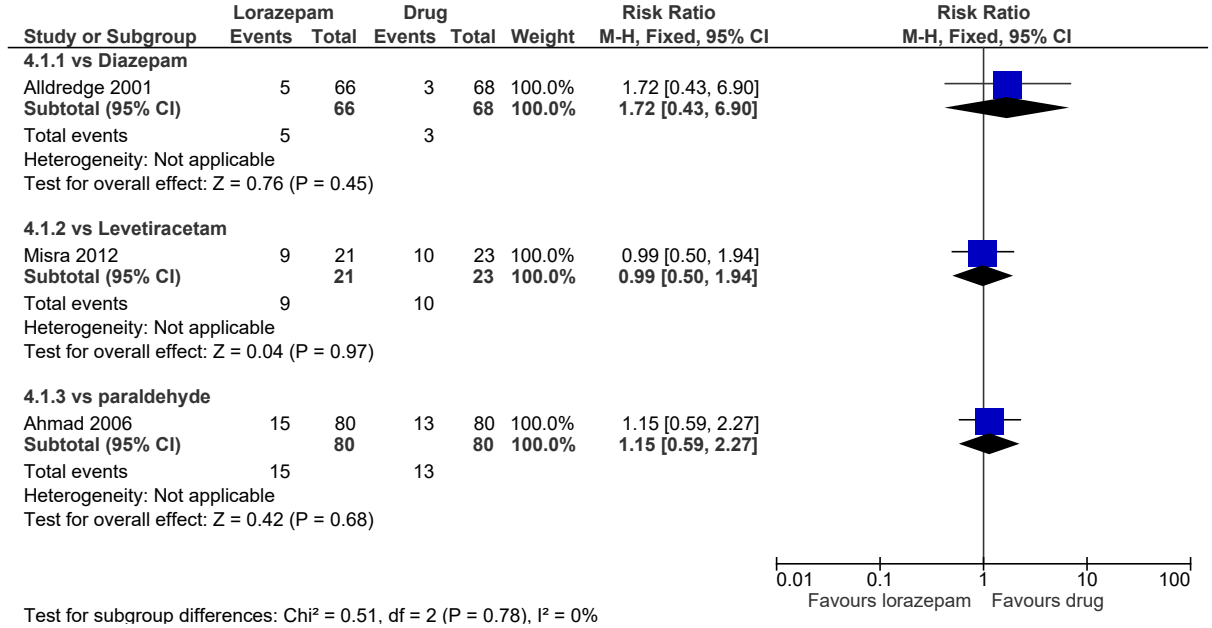


Figure 20: Termination of SE within 10 min

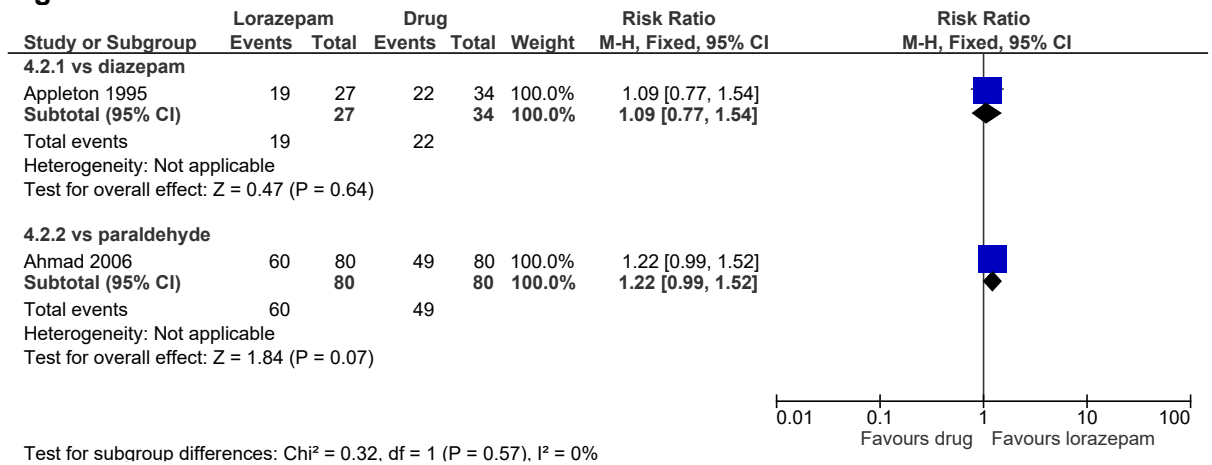
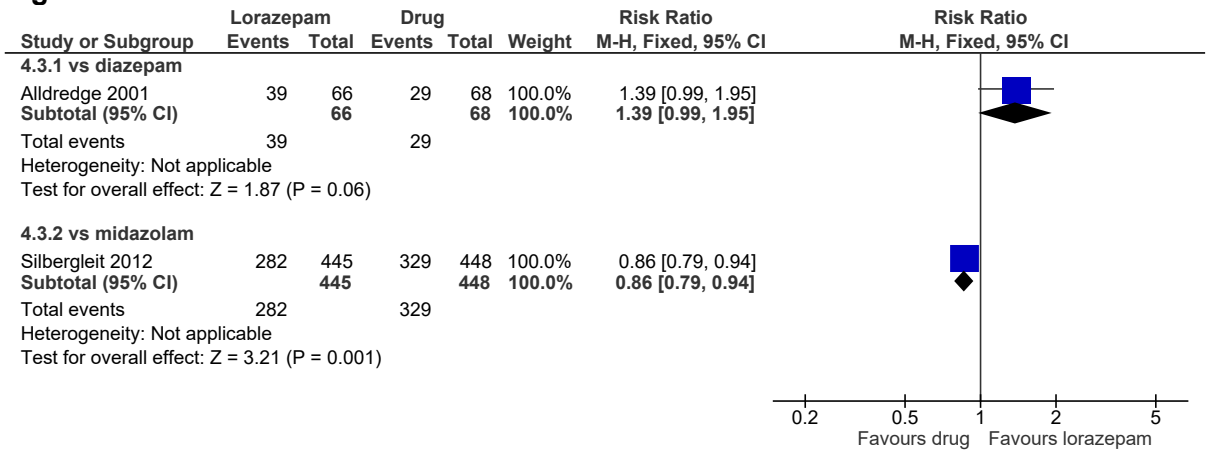


Figure 21: Termination of SE at time of arrival at ED

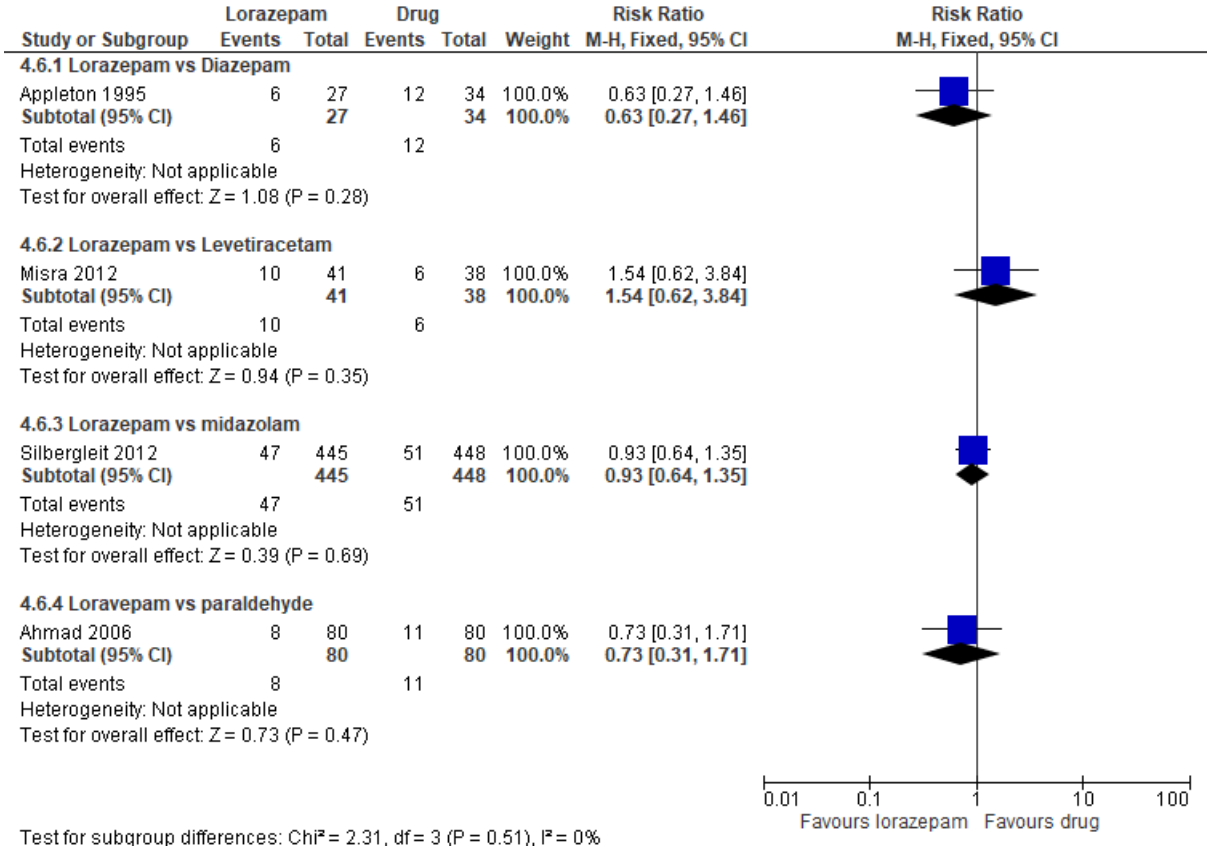


1

Figure 22: Termination of SE within 30 min

2

Figure 23: Seizure recurrence within 24 hours

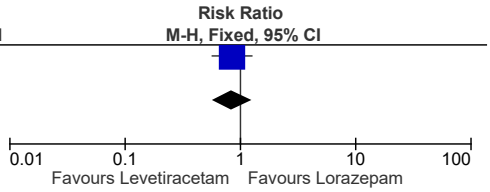


3

Figure 24: Seizure freedom at 24 hours

Study or Subgroup	Lorazepam Events	Total	Levetiracetam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Misra 2012	21	41	23	38	100.0%	0.85 [0.57, 1.25]
Total (95% CI)		**41**		**38**	**100.0%**	**0.85 [0.57, 1.25]**
Total events	21		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)

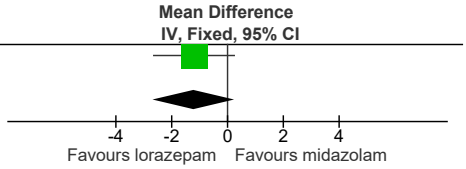


1

Figure 25: Length of hospital stay (days)

Study or Subgroup	Lorazepam Mean	SD	Total	Midazolam Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Silbergleit 2012	5.5	6.4	285	6.7	10	251	100.0%	-1.20 [-2.64, 0.24]
Total (95% CI)			**285**			**251**	**100.0%**	**-1.20 [-2.64, 0.24]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.63 (P = 0.10)

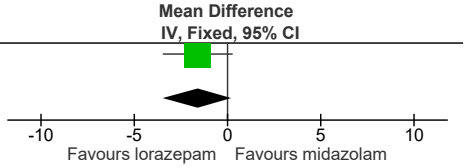


2

Figure 26: Length of ICU stay (days)

Study or Subgroup	Lorazepam Mean	SD	Total	Midazolam Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Silbergleit 2012	4.1	4.7	155	5.7	9.5	123	100.0%	-1.60 [-3.43, 0.23]
Total (95% CI)			**155**			**123**	**100.0%**	**-1.60 [-3.43, 0.23]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.71 (P = 0.09)



3

Figure 27: Adverse events, respiratory failure

Study or Subgroup	Lorazepam Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.7.1 Lorazepam vs Levetiracetam						
Misra 2012	10	21	5	23	100.0%	2.19 [0.89, 5.37]
Subtotal (95% CI)		**21**		**23**	**100.0%**	**2.19 [0.89, 5.37]**
Total events	10		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.09)

Test for subgroup differences: Not applicable

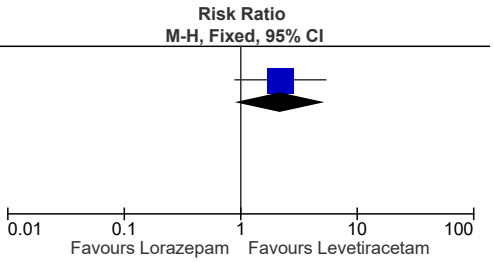
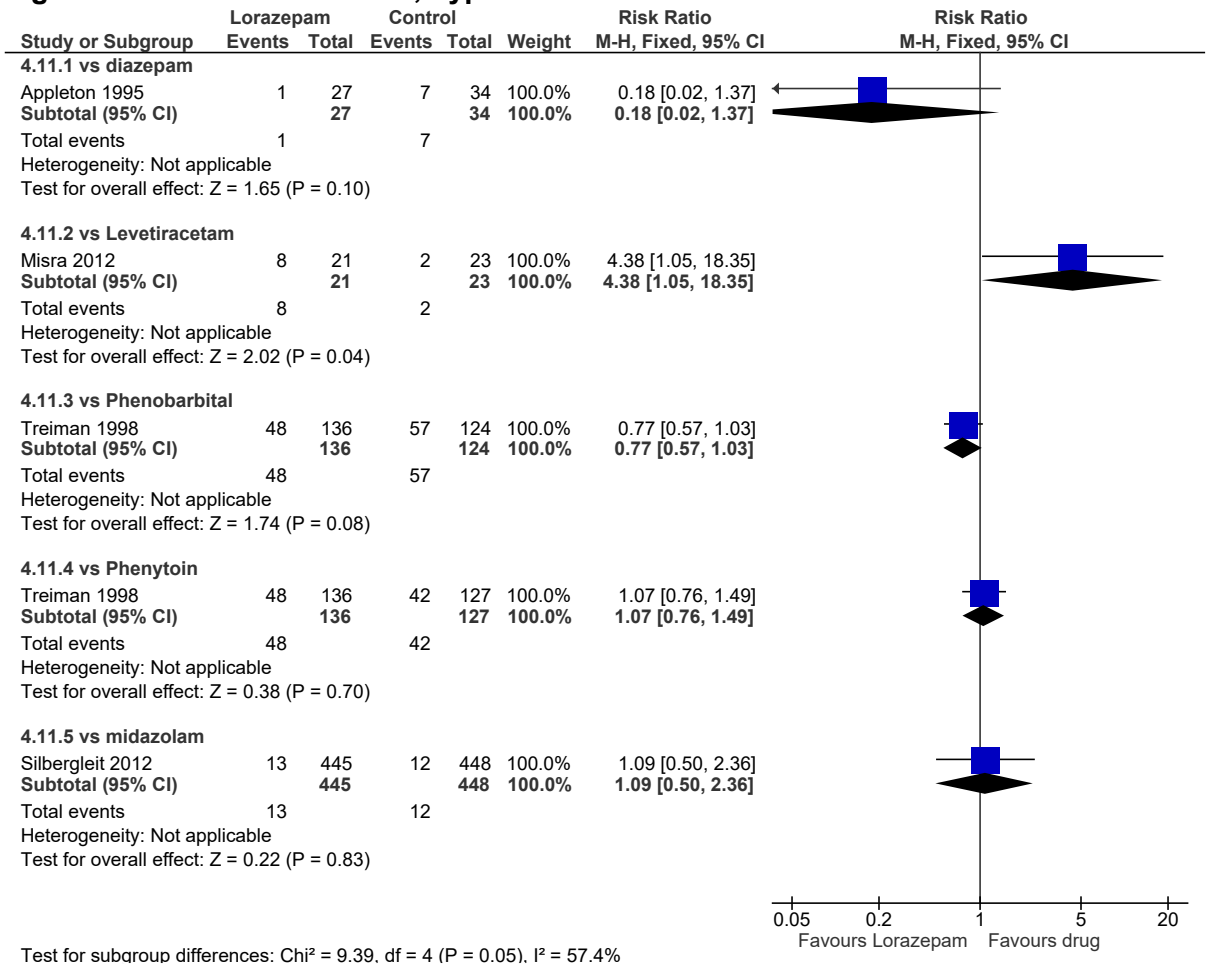


Figure 28: Adverse events, hypotension



E.1.5 Valproate vs phenytoin

Figure 29: Termination of SE after drug infusion

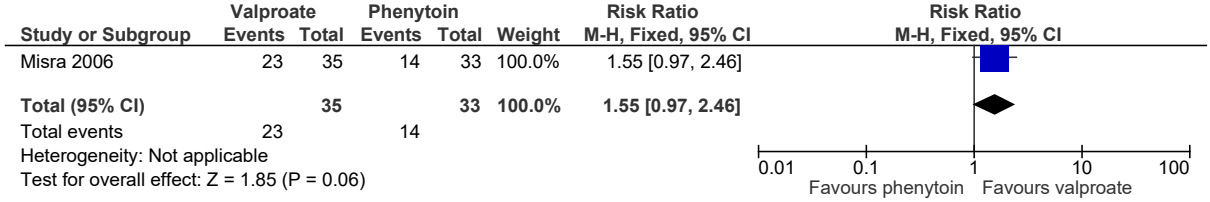


Figure 30: Seizure recurrence within 24 hours

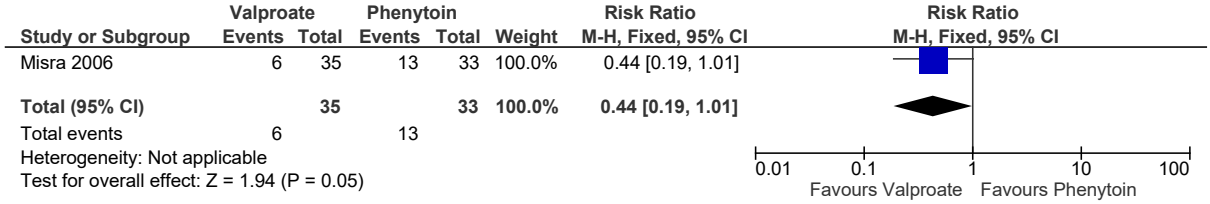


Figure 31: Seizure freedom at 24 hours

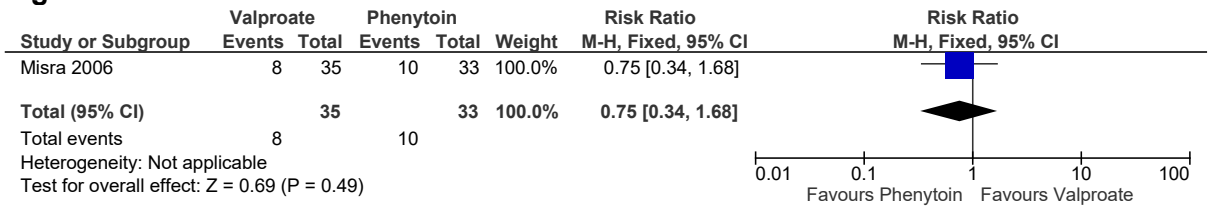
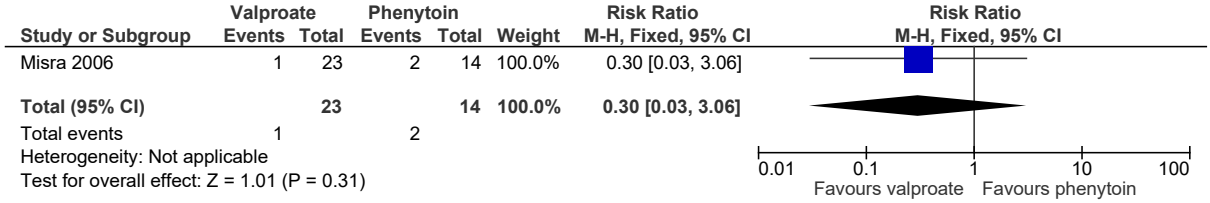
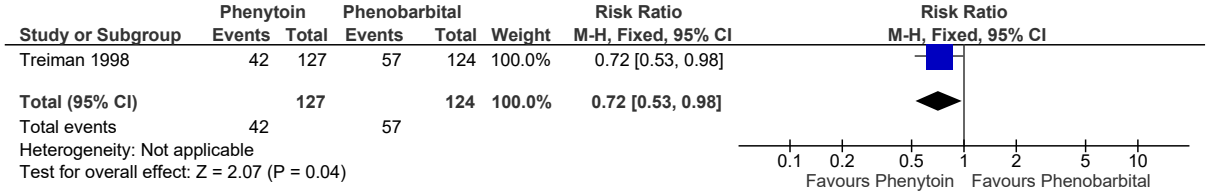


Figure 32: Adverse events, Respiratory depression



E.1.6 Phenytoin vs phenobarbital

Figure 33: Adverse events, hypotension



E.2 Add on Therapy

E.2.1 Valproate vs phenytoin

Figure 34: Mortality

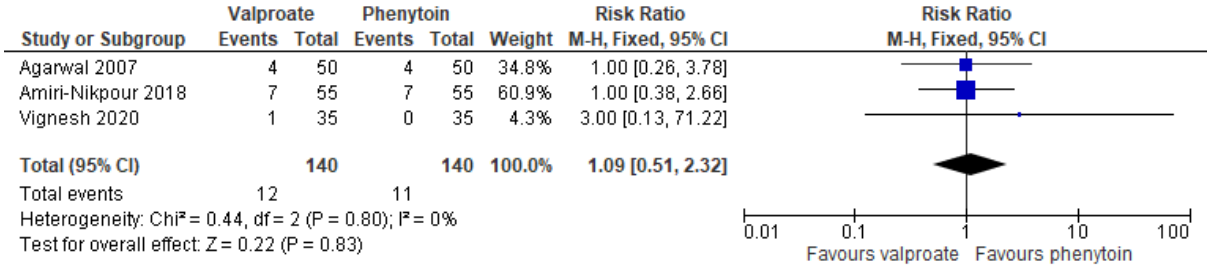


Figure 35: Cessation of SE within 12 min

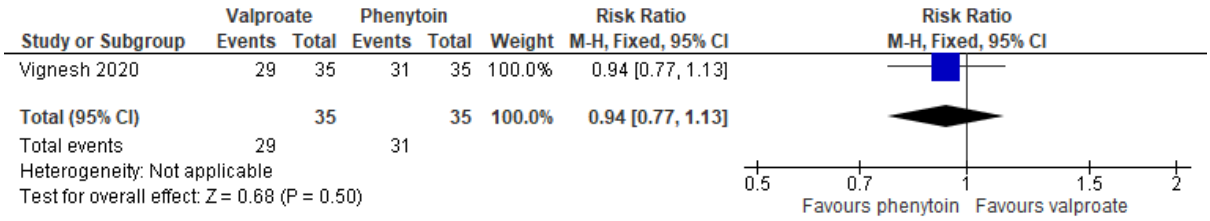
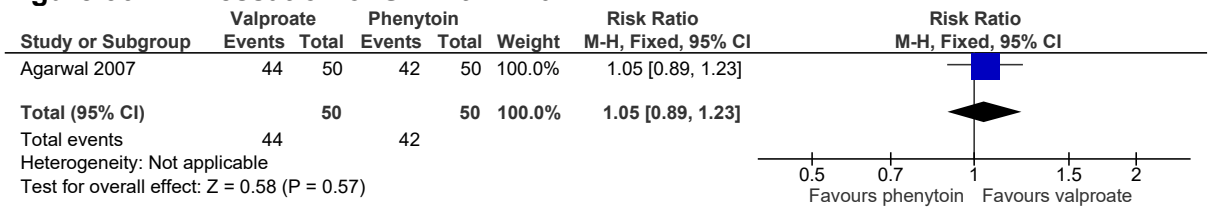
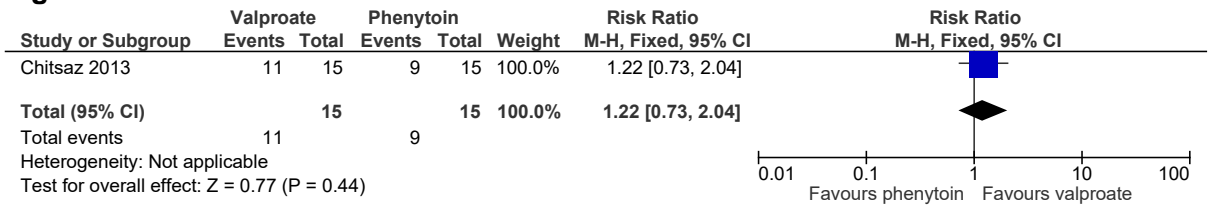


Figure 36: Cessation of SE within 20 min



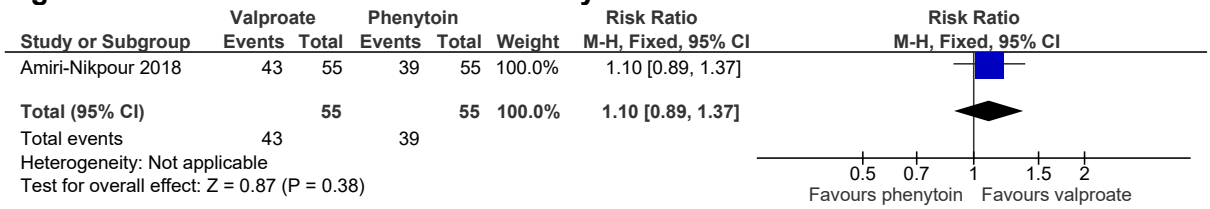
1

Figure 37: Cessation of SE within 12 hours



2

Figure 38: Cessation of SE within 7 days



3

Figure 39: Time to seizure cessation (minutes)

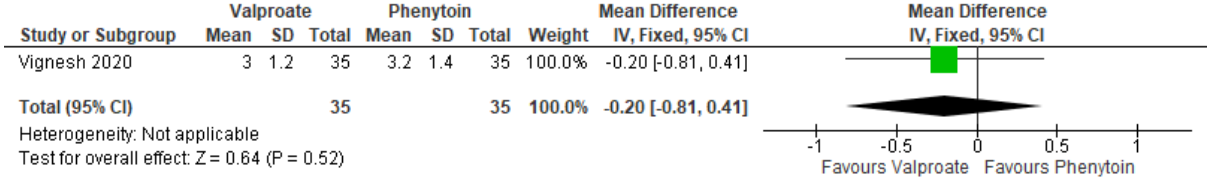
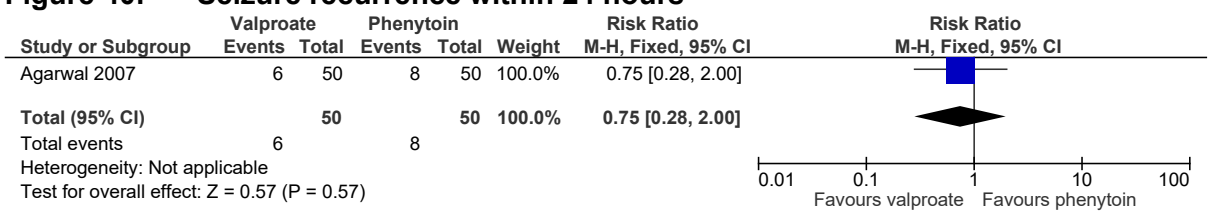


Figure 40: Seizure recurrence within 24 hours



4

Figure 41: Length of hospital stay (days)

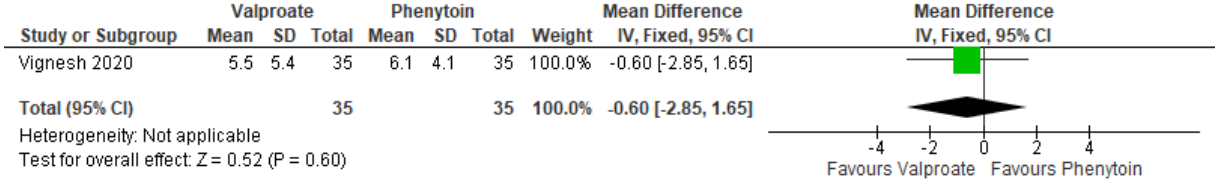


Figure 42: Length of PICU stay (days)

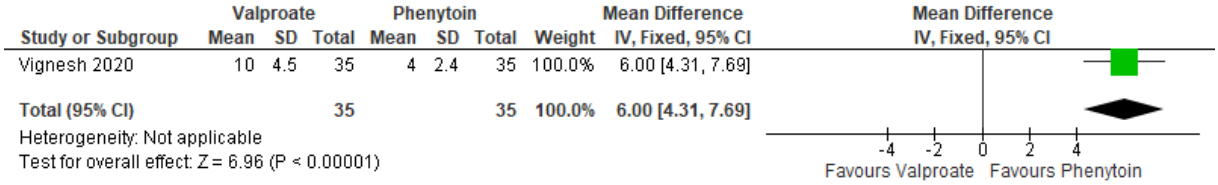


Figure 43: Hypotension

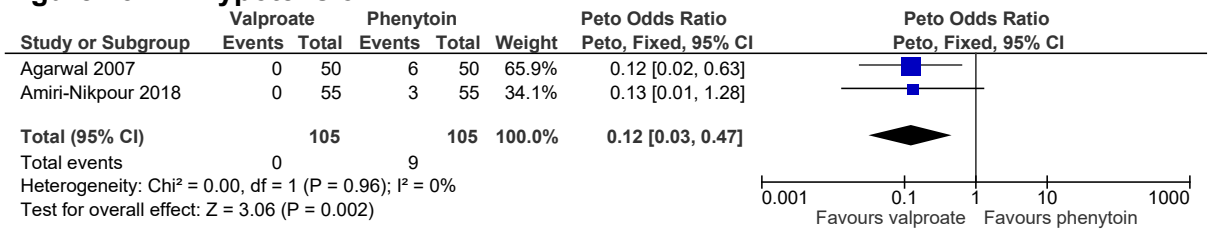
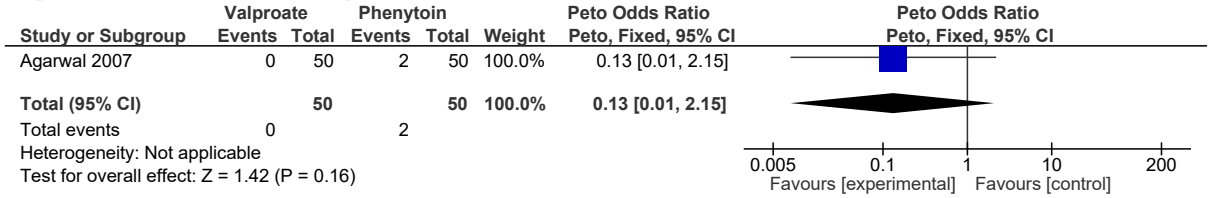


Figure 44: Respiratory depression



E.2.2 Levetiracetam vs phenytoin

Figure 45: Mortality

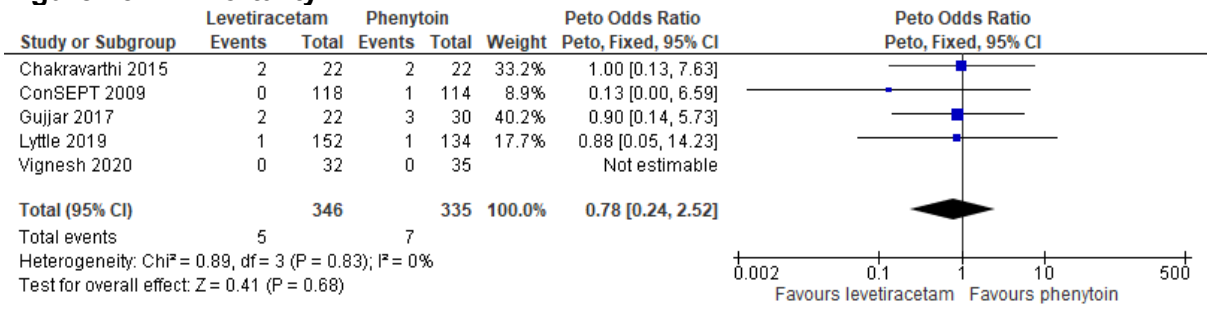


Figure 46: Cessation of SE within 5 min

Study or Subgroup	Levetiracetam Events	Total	Phenytoin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ConSEPT 2009	60	119	68	114	65.9%	0.85 [0.67, 1.07]
Wani 2019	34	52	36	52	34.1%	0.94 [0.72, 1.23]
Total (95% CI)		**171**		**166**	**100.0%**	**0.88 [0.74, 1.05]**
Total events	94		104			

Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)

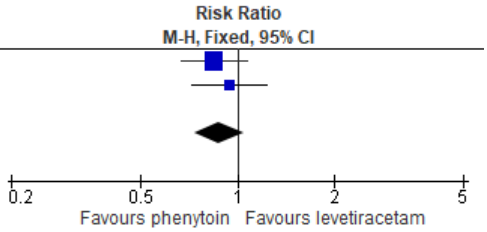


Figure 47: Cessation of SE from 5 – 20 minutes

Study or Subgroup	Levetiracetam Events	Total	Phenytoin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wani 2019	17	52	15	52	100.0%	1.13 [0.64, 2.02]
Total (95% CI)		**52**		**52**	**100.0%**	**1.13 [0.64, 2.02]**
Total events	17		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.67)

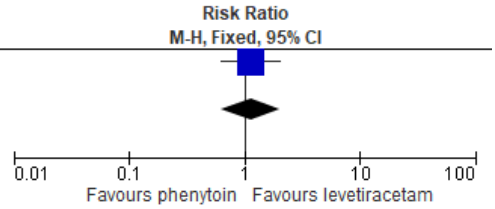


Figure 48: Cessation of SE within 15 minutes

Study or Subgroup	Levetiracetam Events	Total	Phenytoin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vignesh 2020	30	32	31	35	100.0%	1.06 [0.91, 1.23]
Total (95% CI)		**32**		**35**	**100.0%**	**1.06 [0.91, 1.23]**
Total events	30		31			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)

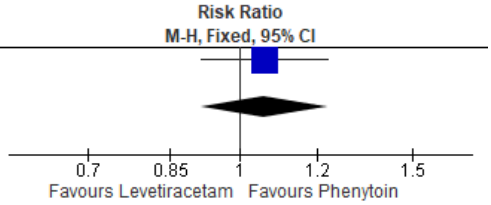


Figure 49: Cessation of SE from 20 – 40 minutes

Study or Subgroup	Levetiracetam Events	Total	Phenytoin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wani 2019	1	52	1	52	100.0%	1.00 [0.06, 15.57]
Total (95% CI)		**52**		**52**	**100.0%**	**1.00 [0.06, 15.57]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

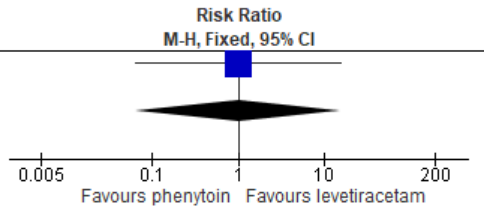


Figure 50: Cessation of SE within 30 minutes

Study or Subgroup	Levetiracetam Events	Total	Phenytoin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chakravarthi 2015	13	22	15	22	5.7%	0.87 [0.55, 1.36]
Noureen 2019	278	300	250	300	94.3%	1.11 [1.05, 1.18]
Total (95% CI)		**322**		**322**	**100.0%**	**1.10 [1.03, 1.17]**
Total events	291		265			

Heterogeneity: Chi² = 1.23, df = 1 (P = 0.27); I² = 19%
Test for overall effect: Z = 3.00 (P = 0.003)

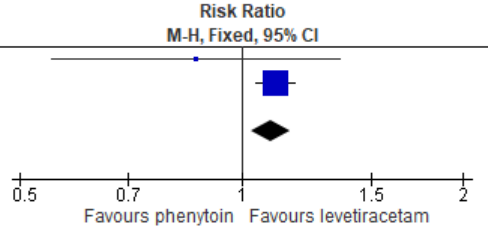


Figure 51: Cessation of SE within 2 hours

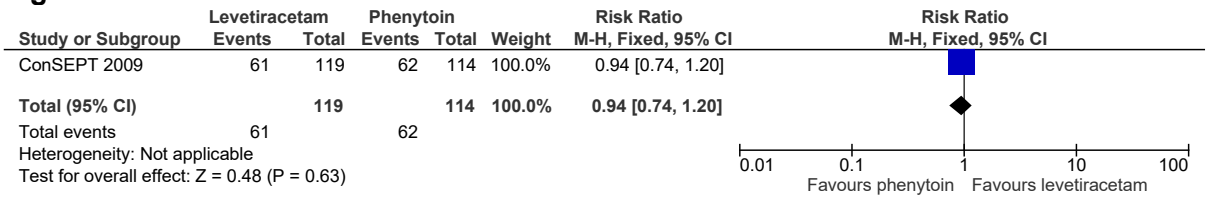


Figure 52: Cessation of SE within 24 h

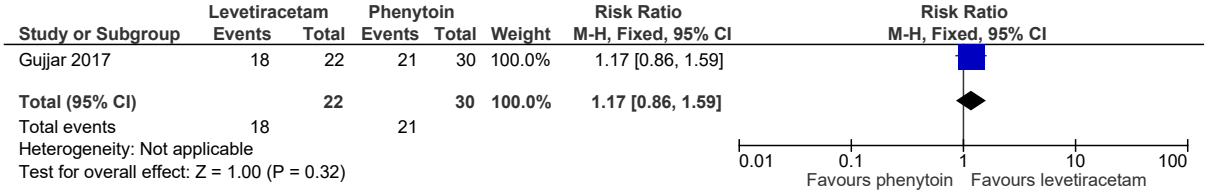


Figure 53: Recurrence of seizure within 24 hours

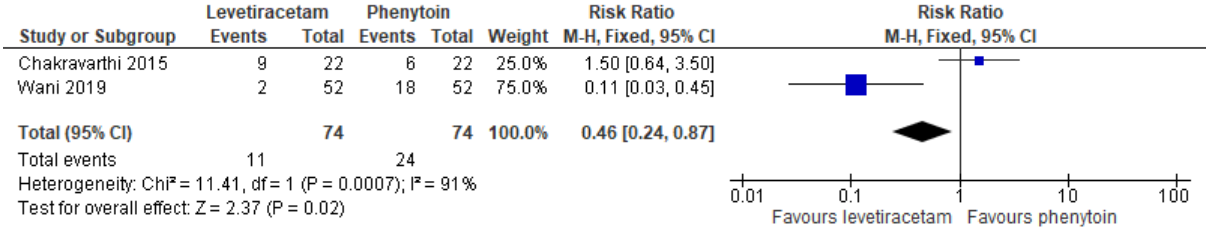


Figure 54: Time to seizure cessation

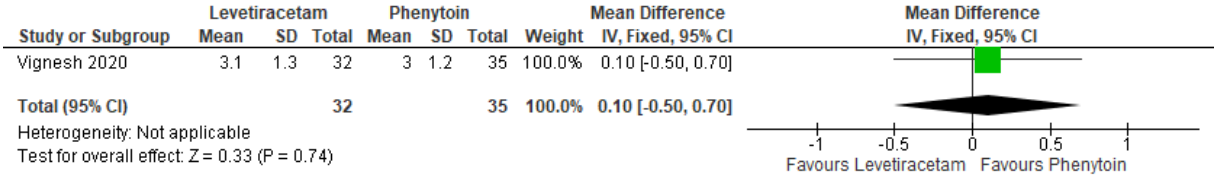


Figure 55: Mean duration of SE of good responders

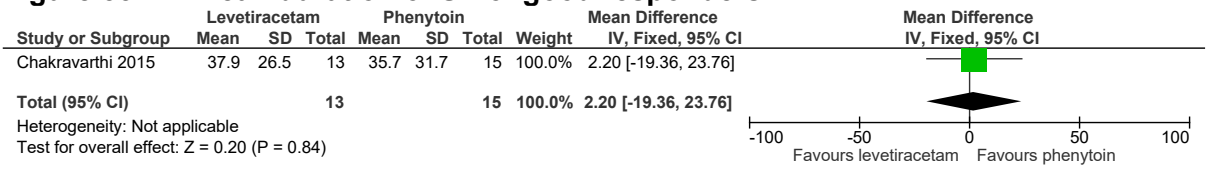


Figure 56: Good outcome at discharge (FIM score)

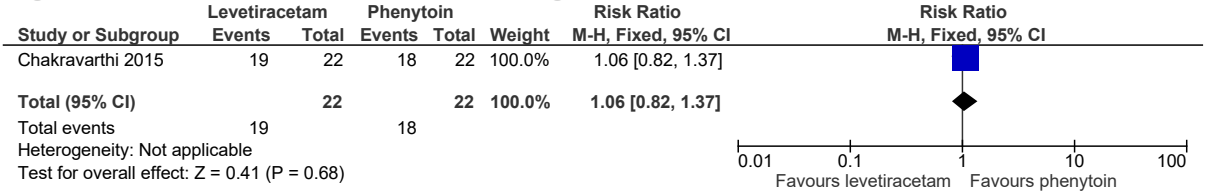
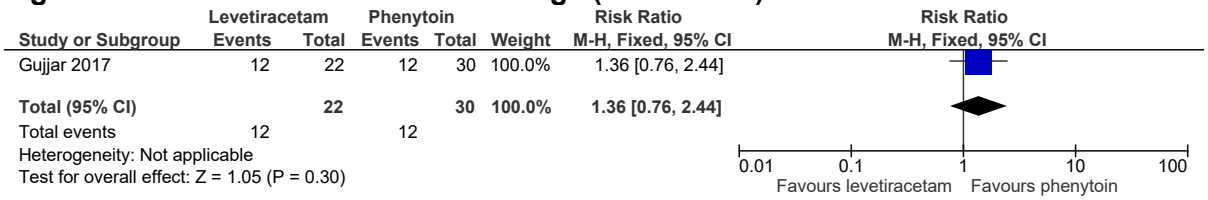


Figure 57: Good outcome at discharge (mRS score)



1

Figure 58: Mean length of hospital stay

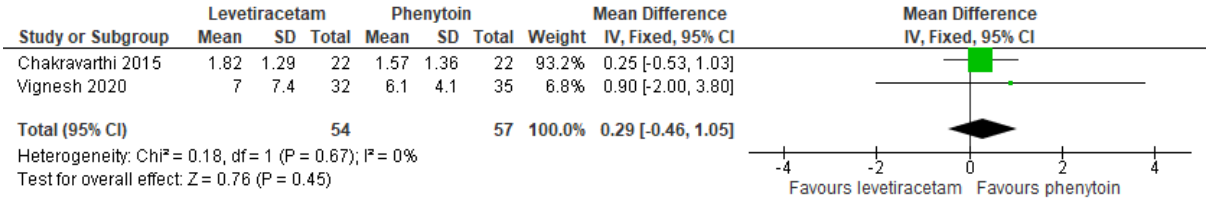


Figure 59: Mean length of PICU stay

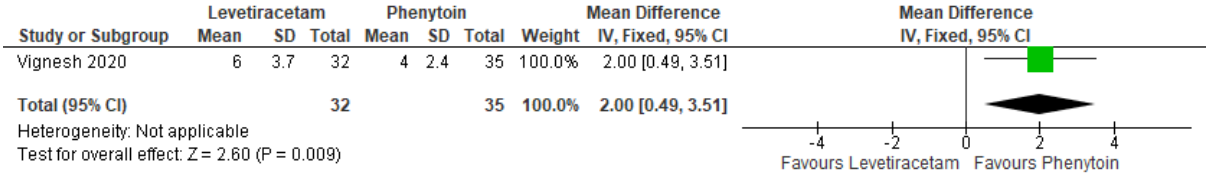


Figure 60: Admission to critical care

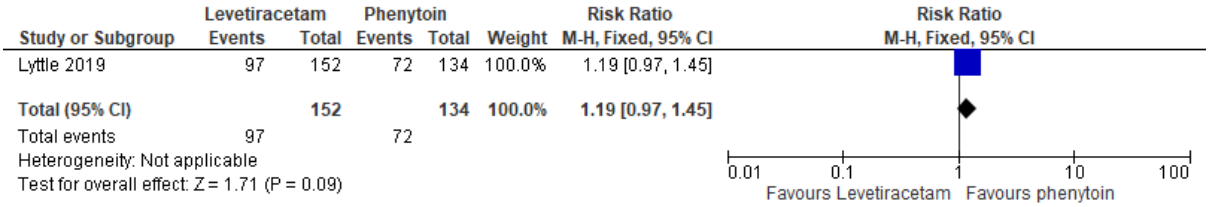
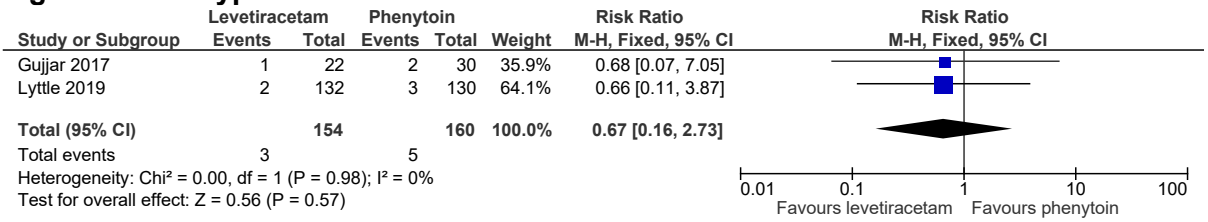


Figure 61: Hypotension



2

Figure 62: Adverse events, confusion

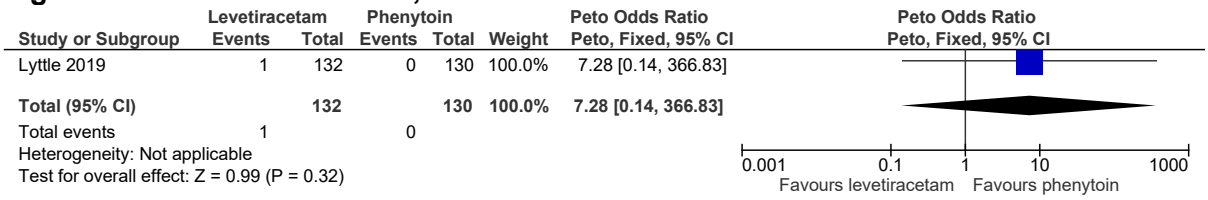


Figure 63: Cardiac depression

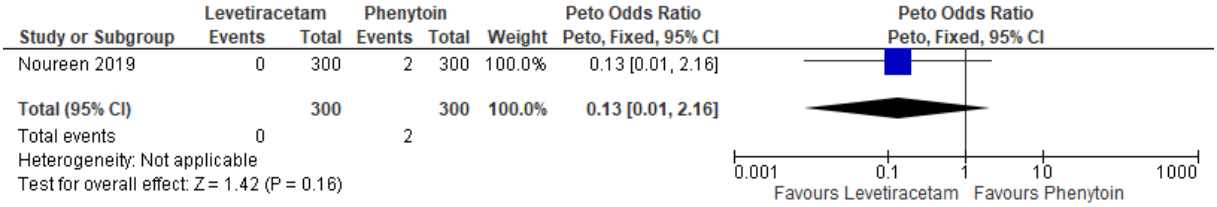
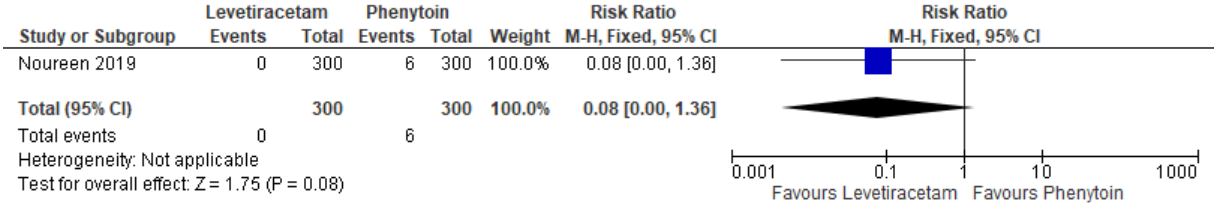


Figure 64: Respiratory depression



E.2.3 Lignocaine vs midazolam

Figure 65: Cessation of SE

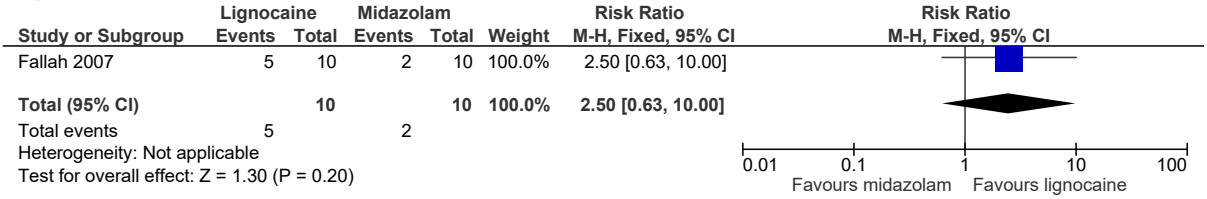


Figure 66: Length of ICU stay

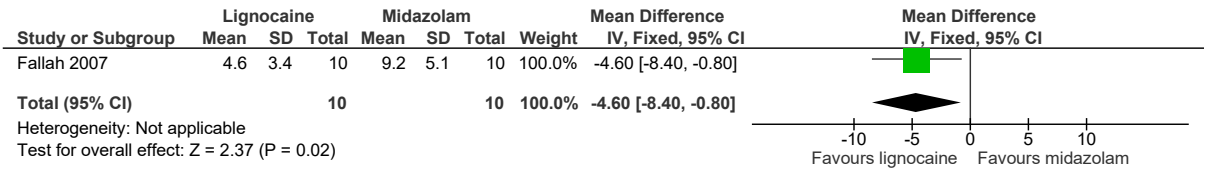
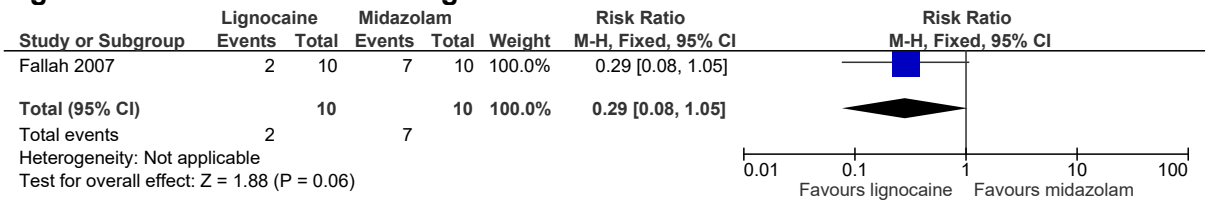


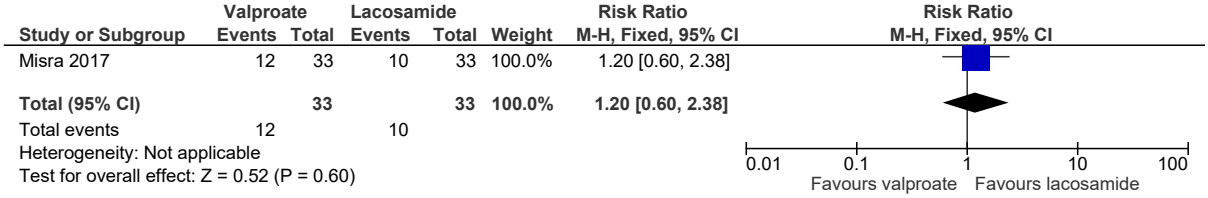
Figure 67: Intubation needing mechanical ventilation



1

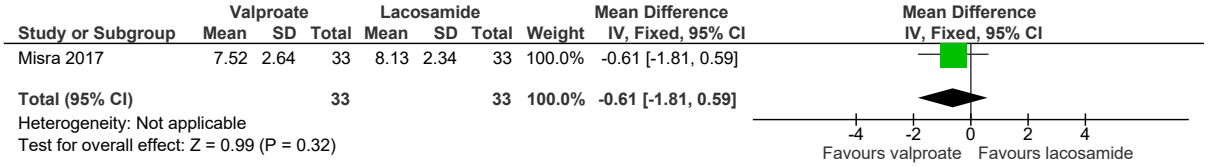
2 E.2.4 Valproate vs lacosamide

Figure 68: Mortality



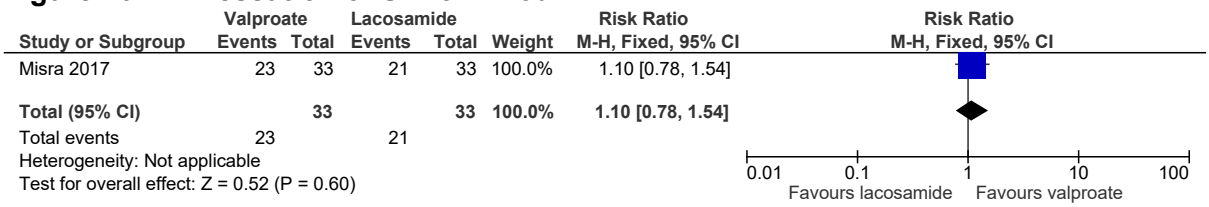
3

Figure 69: Time for seizure cessation after drug administration (min)



4

Figure 70: Cessation of SE for 1 hour



5

Figure 71: Seizure freedom within 24 hours

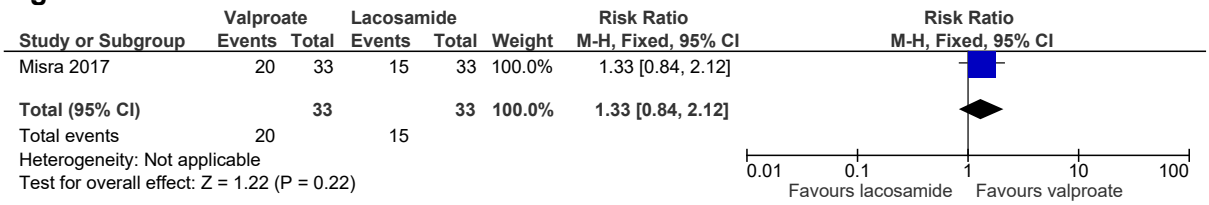
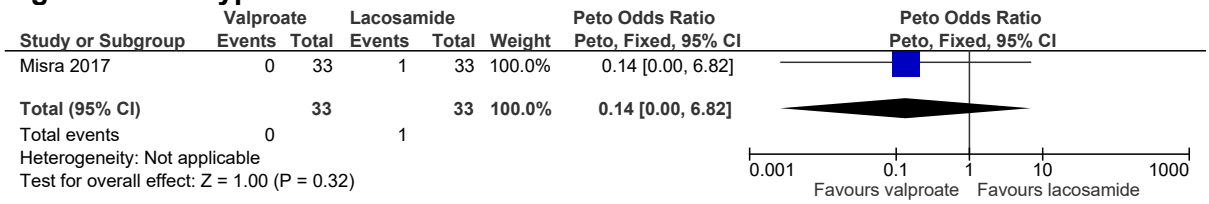


Figure 72: Hypotension



E.2.5 Midazolam vs diazepam

Figure 73: Mortality

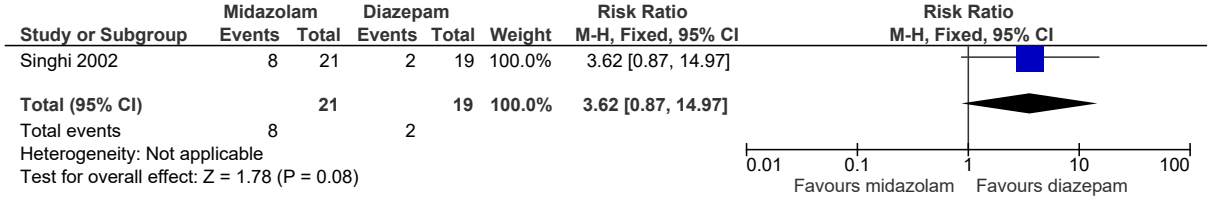


Figure 74: Time to initial seizure cessation (min)

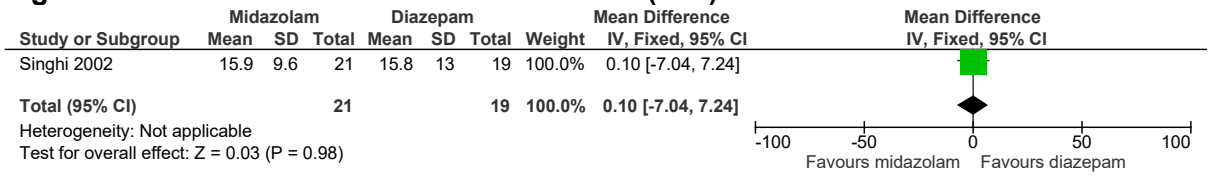


Figure 75: Time to final seizure cessation (min)

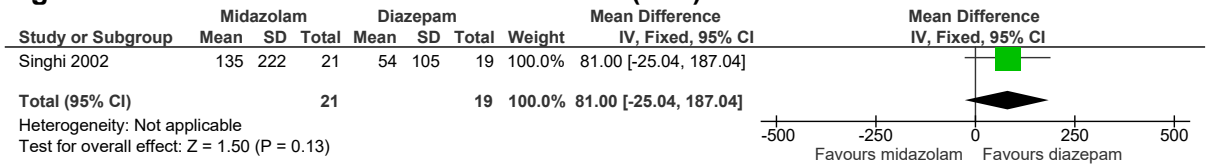


Figure 76: Cessation of SE within 12 hours (6 hours)

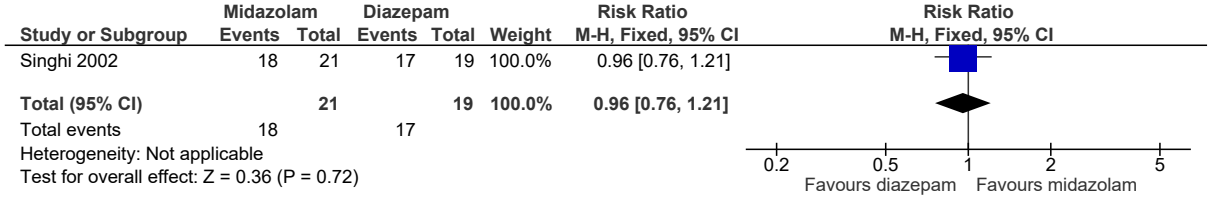
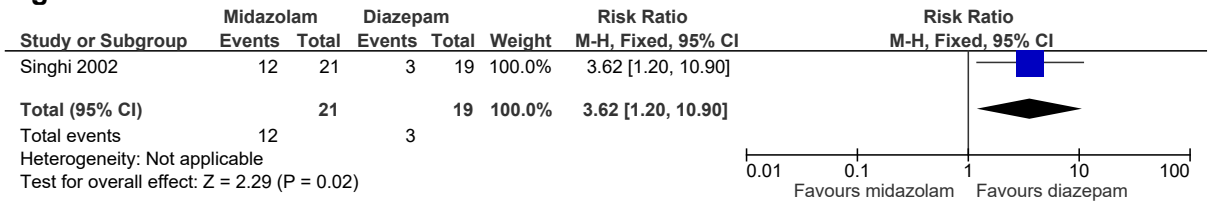


Figure 77: Seizure recurrence whilst on infusion

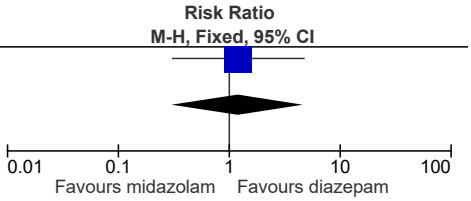


1

Figure 78: Seizure recurrence after stopping infusion

Study or Subgroup	Midazolam Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Singhi 2002	4	21	3	19	100.0%	1.21 [0.31, 4.71]
Total (95% CI)		**21**		**19**	**100.0%**	**1.21 [0.31, 4.71]**
Total events	4		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)

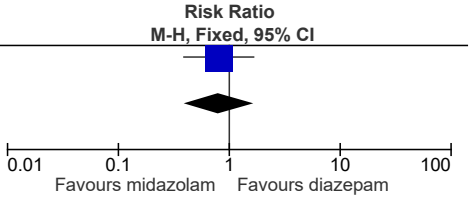


2

Figure 79: Hypotension

Study or Subgroup	Midazolam Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Singhi 2002	8	21	9	19	100.0%	0.80 [0.39, 1.66]
Total (95% CI)		**21**		**19**	**100.0%**	**0.80 [0.39, 1.66]**
Total events	8		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.55)

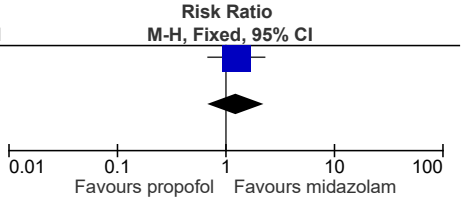


3 ## E.2.6 Propofol vs midazolam

Figure 80: Mortality

Study or Subgroup	Propofol Events	Total	Midazolam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Masapu 2018	8	11	7	12	100.0%	1.25 [0.68, 2.27]
Total (95% CI)		**11**		**12**	**100.0%**	**1.25 [0.68, 2.27]**
Total events	8		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

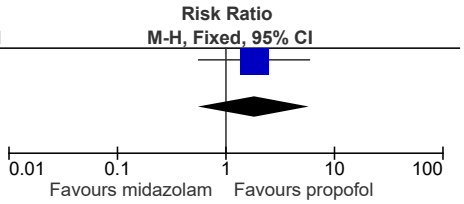


4

Figure 81: Cessation of SE for 48 hours

Study or Subgroup	Propofol Events	Total	Midazolam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Masapu 2018	5	11	3	12	100.0%	1.82 [0.56, 5.88]
Total (95% CI)		**11**		**12**	**100.0%**	**1.82 [0.56, 5.88]**
Total events	5		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

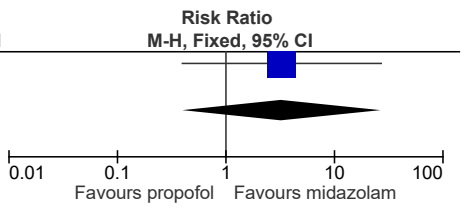


5

Figure 82: Hypotension

Study or Subgroup	Propofol Events	Total	Midazolam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Masapu 2018	3	11	1	12	100.0%	3.27 [0.40, 27.00]
Total (95% CI)		**11**		**12**	**100.0%**	**3.27 [0.40, 27.00]**
Total events	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)



E.2.7 Phenobarbital vs valproate

Figure 83: Mortality

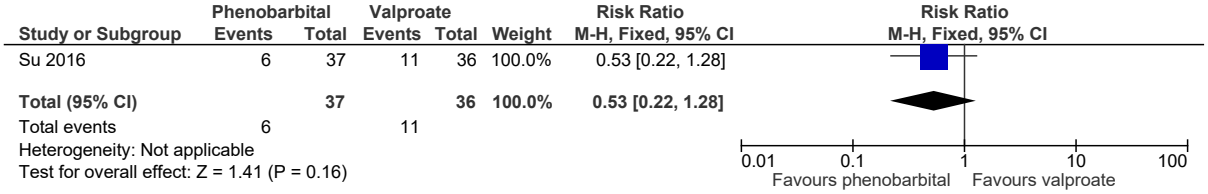


Figure 84: Seizure control within 20 min

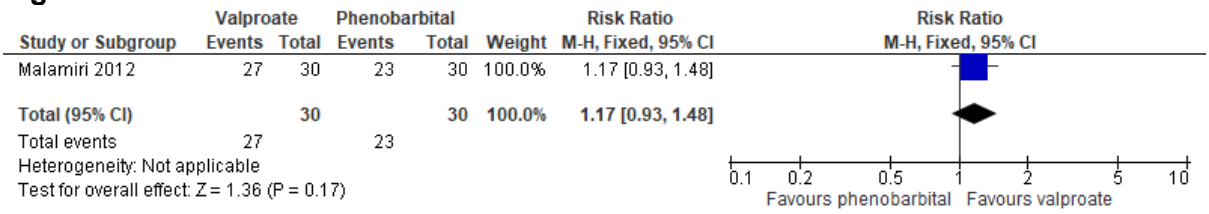
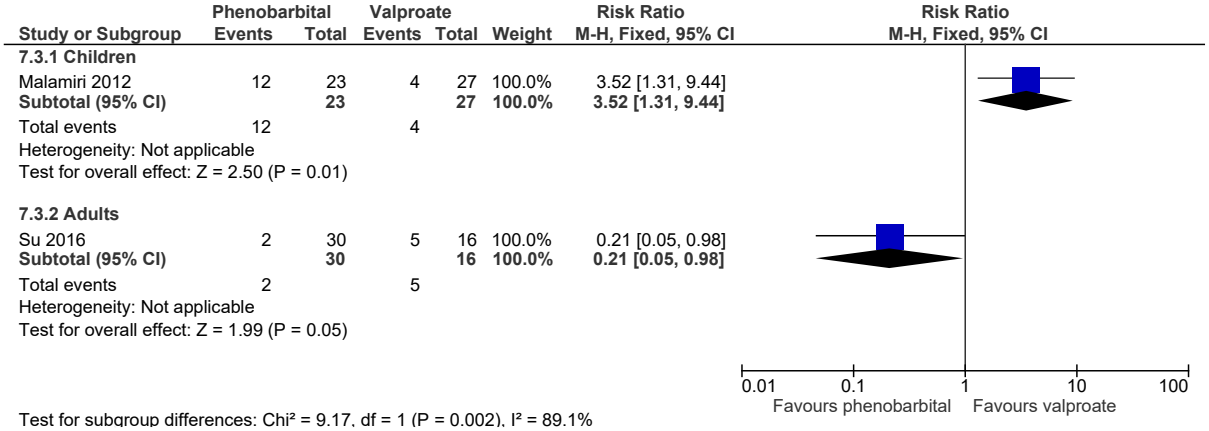
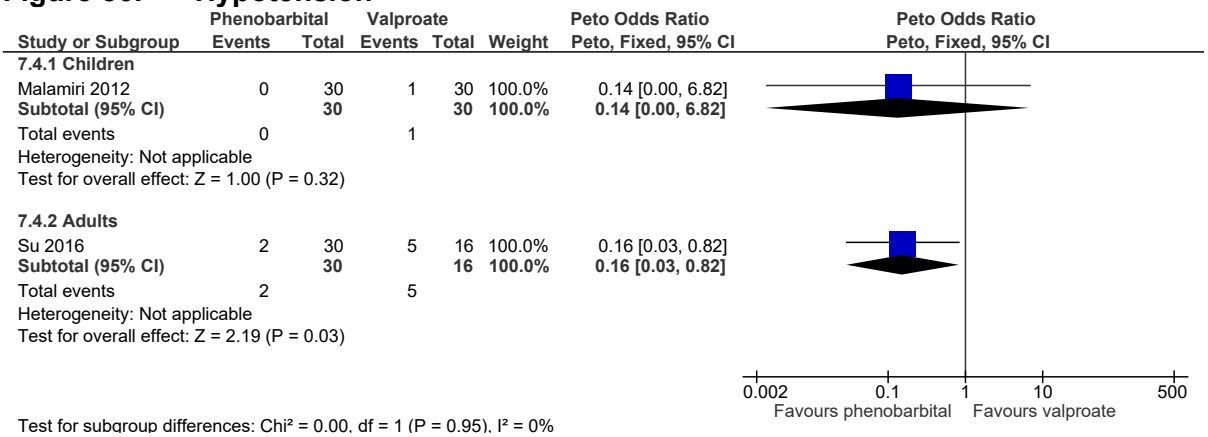


Figure 85: Recurrence of seizure within 24 hours



Test for subgroup differences: Chi² = 9.17, df = 1 (P = 0.002), I² = 89.1%

Figure 86: Hypotension

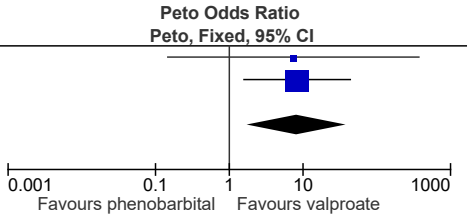


Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%

Figure 87: Transient depressed respiration

Study or Subgroup	Phenobarbital Events	Total	Valproate Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Malamiri 2012	1	30	0	30	15.2%	7.39 [0.15, 372.38]
Su 2016	6	37	0	36	84.8%	8.33 [1.59, 43.79]
Total (95% CI)		**67**		**66**	**100.0%**	**8.18 [1.78, 37.71]**
Total events	7		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)



E.2.8 Valproate vs diazepam

Figure 88: Mortality

Study or Subgroup	Valproate Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2011	5	30	2	35	100.0%	2.92 [0.61, 13.96]
Total (95% CI)		**30**		**35**	**100.0%**	**2.92 [0.61, 13.96]**
Total events	5		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)

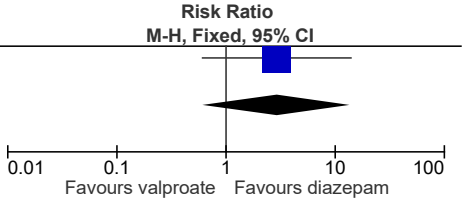


Figure 89: Cessation of SE within 30 min

Study or Subgroup	Valproate Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mehta 2007	16	20	17	20	100.0%	0.94 [0.71, 1.25]
Total (95% CI)		**20**		**20**	**100.0%**	**0.94 [0.71, 1.25]**
Total events	16		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)

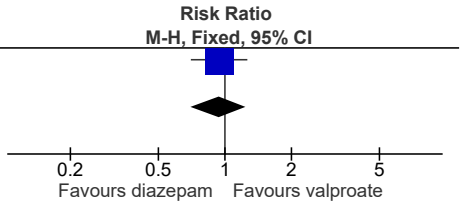


Figure 90: Cessation of SE within 1 hour

Study or Subgroup	Valproate Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2011	15	30	20	36	100.0%	0.90 [0.57, 1.43]
Total (95% CI)		**30**		**36**	**100.0%**	**0.90 [0.57, 1.43]**
Total events	15		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)

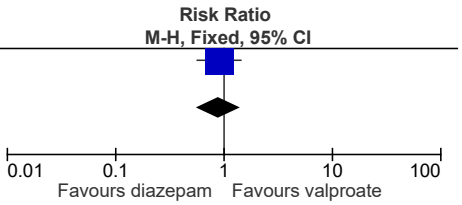


Figure 91: Time for seizure cessation after drug administration (min)

Study or Subgroup	Valproate Mean	SD	Total	Diazepam Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mehta 2007	8.8	7.4	20	26.6	26.7	20	100.0%	-17.80 [-29.94, -5.66]
Total (95% CI)			**20**			**20**	**100.0%**	**-17.80 [-29.94, -5.66]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.87 (P = 0.004)

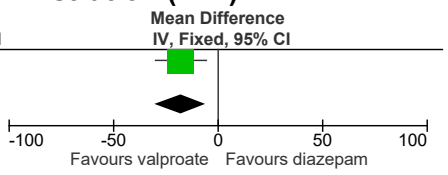
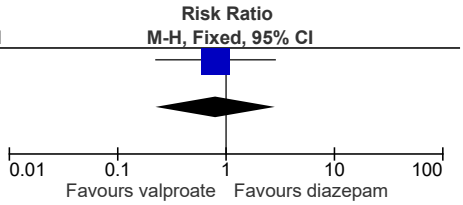


Figure 92: Recurrence of seizure within 24 hours

Study or Subgroup	Valproate Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2011	3	15	5	20	100.0%	0.80 [0.23, 2.83]
Total (95% CI)		**15**		**20**	**100.0%**	**0.80 [0.23, 2.83]**
Total events	3		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)

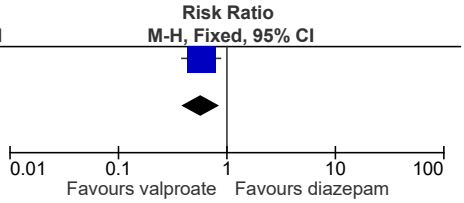


1

Figure 93: ICU admission

Study or Subgroup	Valproate Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mehta 2007	11	20	19	20	100.0%	0.58 [0.38, 0.87]
Total (95% CI)		**20**		**20**	**100.0%**	**0.58 [0.38, 0.87]**
Total events	11		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.62 (P = 0.009)

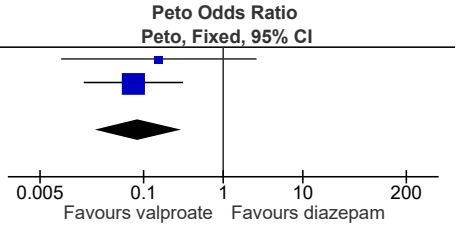


2

Figure 94: Hypotension

Study or Subgroup	Valproate Events	Total	Diazepam Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chen 2011	0	30	2	36	20.2%	0.16 [0.01, 2.57]
Mehta 2007	0	20	10	20	79.8%	0.07 [0.02, 0.31]
Total (95% CI)		**50**		**56**	**100.0%**	**0.09 [0.02, 0.30]**
Total events	0		12			

Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 3.81 (P = 0.0001)

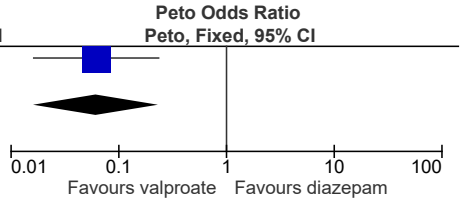


3

Figure 95: Respiratory depression

Study or Subgroup	Valproate Events	Total	Diazepam Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Mehta 2007	0	20	12	20	100.0%	0.06 [0.02, 0.23]
Total (95% CI)		**20**		**20**	**100.0%**	**0.06 [0.02, 0.23]**
Total events	0		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.09 (P < 0.0001)

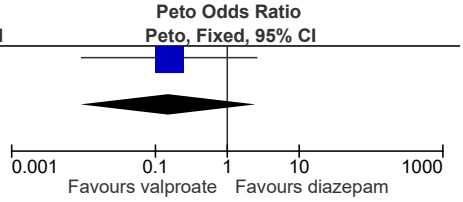


4

Figure 96: Need for intubation

Study or Subgroup	Valproate Events	Total	Diazepam Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chen 2011	0	30	2	36	100.0%	0.16 [0.01, 2.57]
Total (95% CI)		**30**		**36**	**100.0%**	**0.16 [0.01, 2.57]**
Total events	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)



E.2.9 Levetiracetam vs Fosphenytoin

Figure 97: Mortality

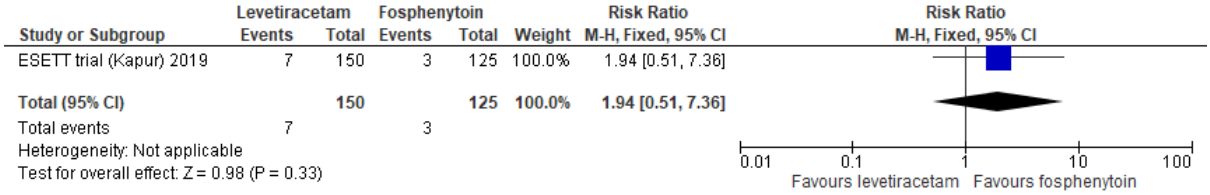


Figure 98: Cessation of SE from 10 – 20 minutes

Figure 99: Cessation of SE within 5 minutes

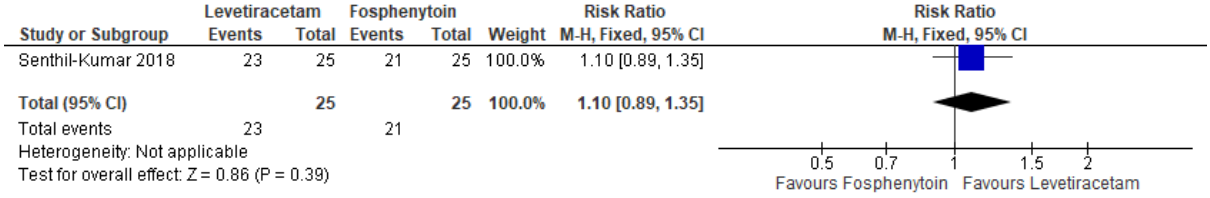


Figure 100: Cessation of SE (& improvement in consciousness at 60 min without other anticonvulsant medications)

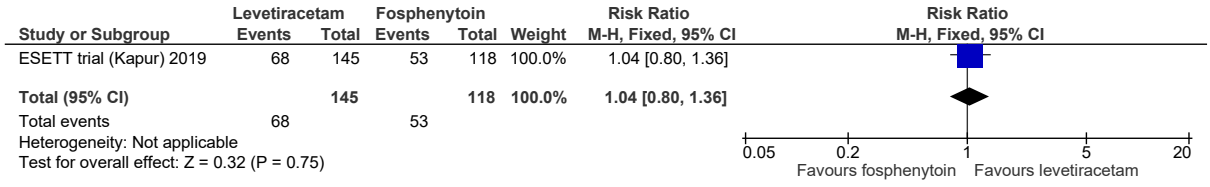


Figure 101: Time to seizure cessation

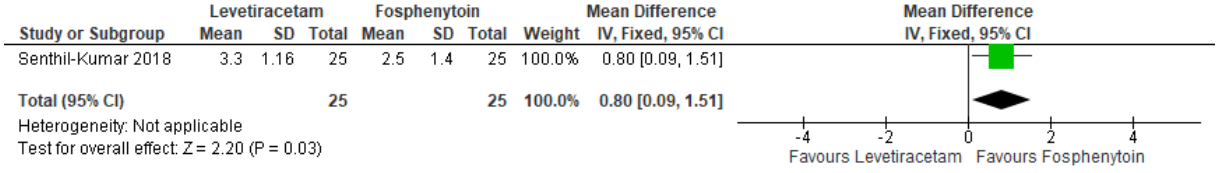


Figure 102: Seizure recurrence within 24 hours (within 60 min to 12 hours after start of trial drug infusion)

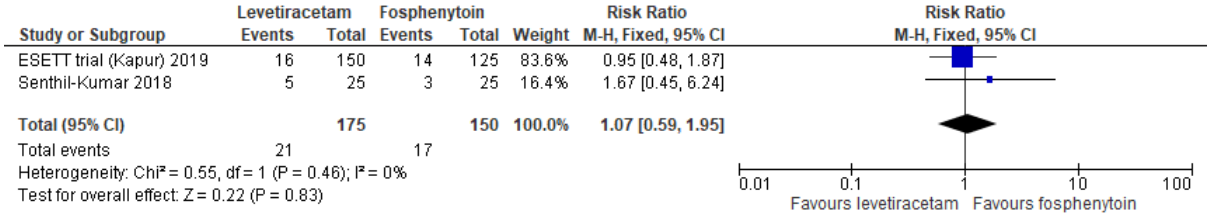


Figure 103: Seizure recurrence within 48 hours

Figure 104: Length of hospital stay

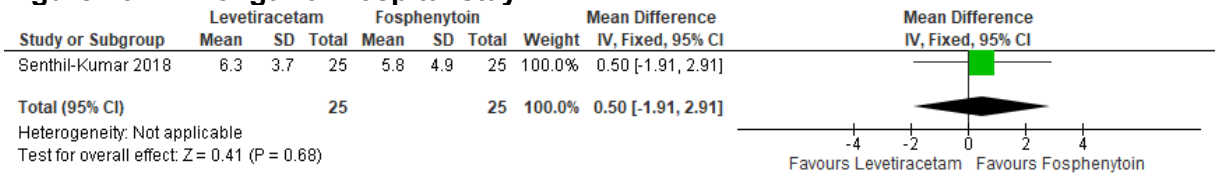


Figure 105: Length of PICU stay

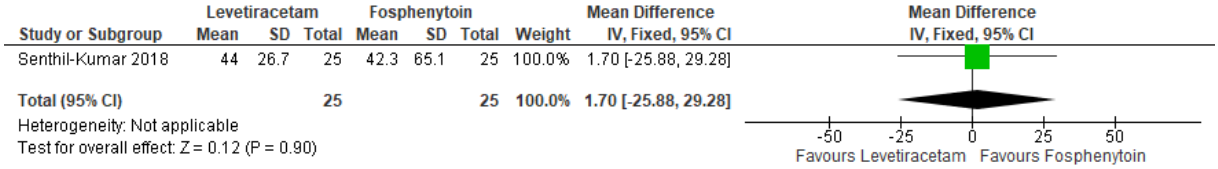


Figure 106: ICU admission

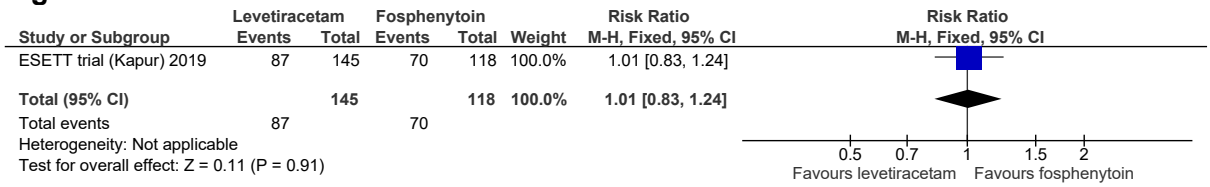


Figure 107: Hypotension (defined as life threatening, within 60 min after start of trial-drug infusion)

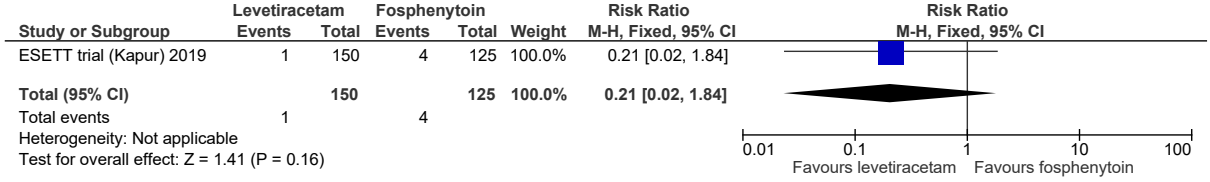


Figure 108: Respiratory depression

Figure 109: Bradycardia

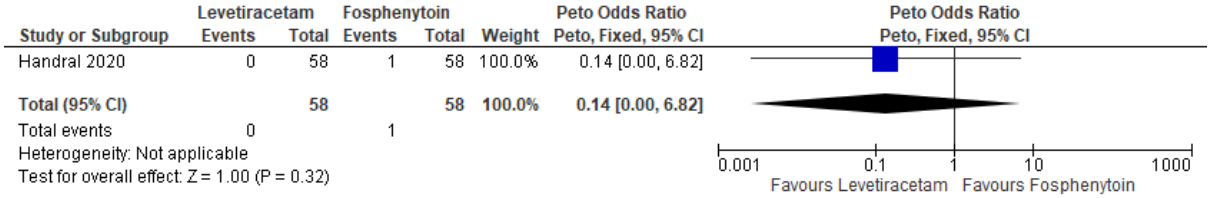
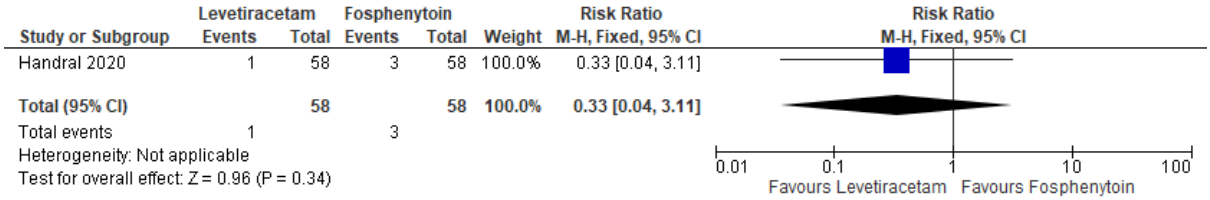


Figure 110: Tracheal Intubation



E.2.10 Levetiracetam vs valproate

Figure 111: Mortality

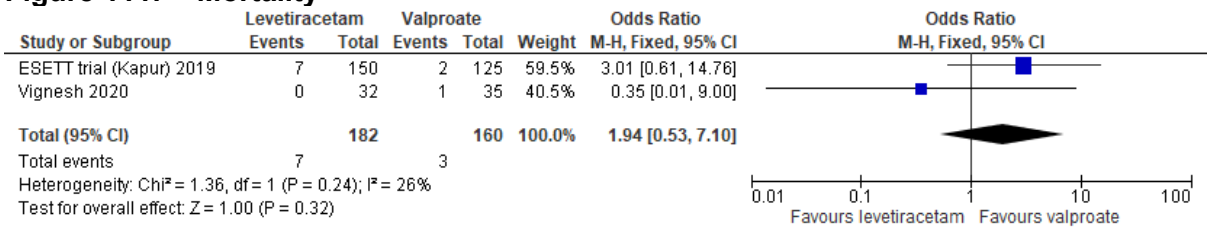


Figure 112: Cessation of SE within 15 minutes

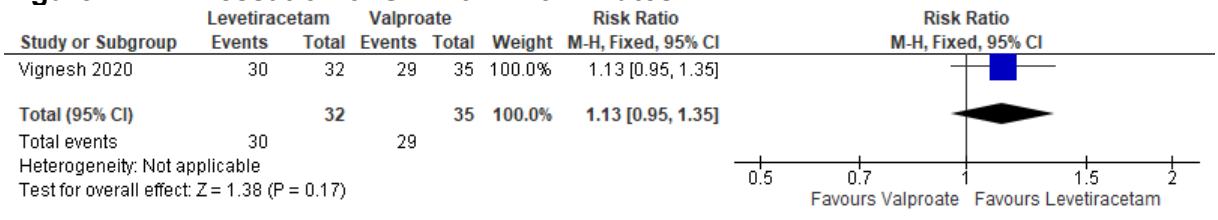


Figure 113: Time to seizure cessation

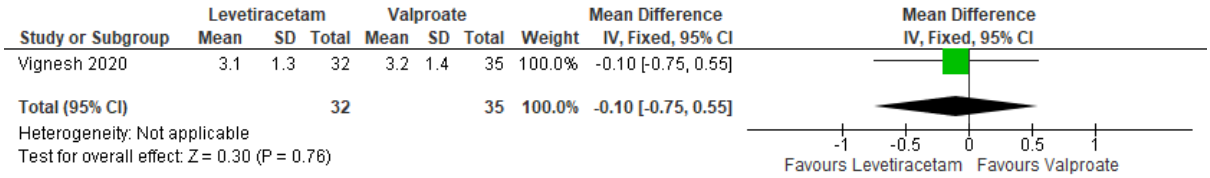
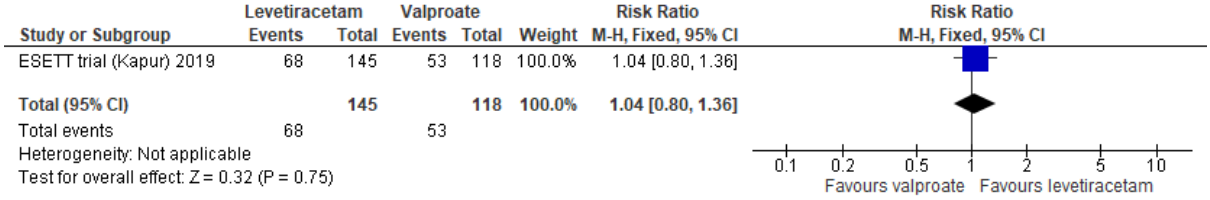
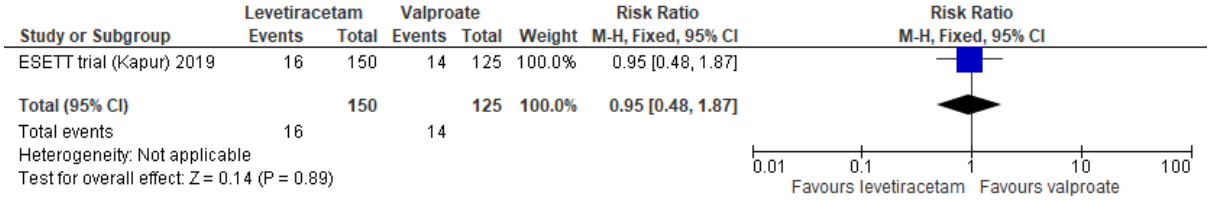


Figure 114: Cessation of SE (& improvement in consciousness at 60 min without other anticonvulsant medications)



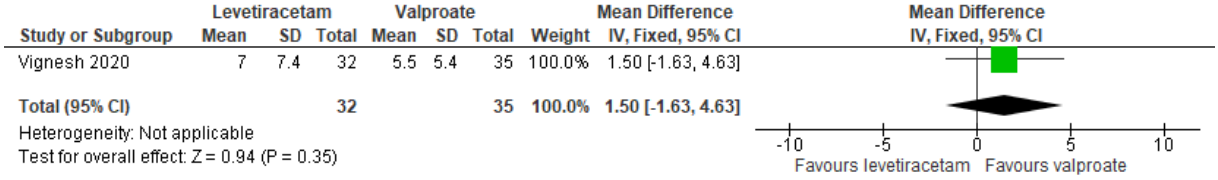
1

Figure 115: Seizure recurrence within 24 hours (within 60 min to 12 hours after start of trial drug infusion)



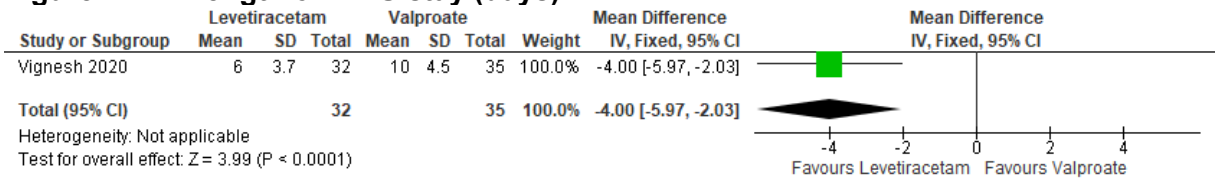
2

Figure 116: length of hospital stay (days)



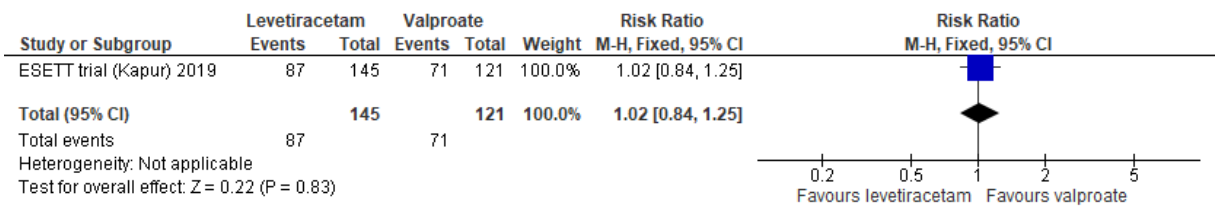
3
4
5

Figure 117: length of PICU stay (days)



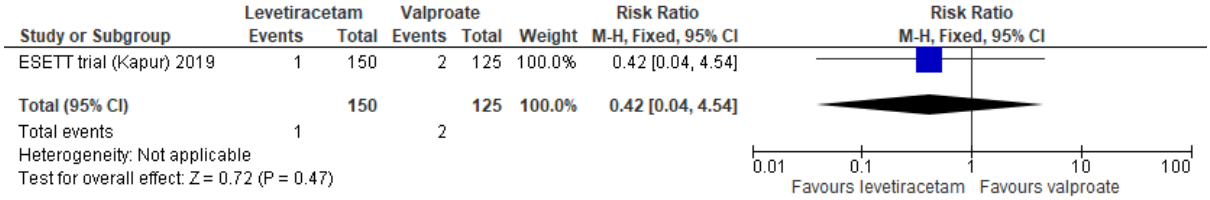
6

Figure 118: ICU admission



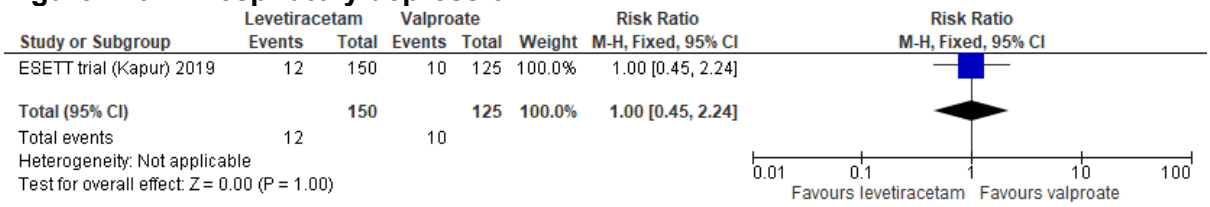
7

Figure 119: Hypotension (defined as life threatening, within 60 min after start of trial-drug infusion)



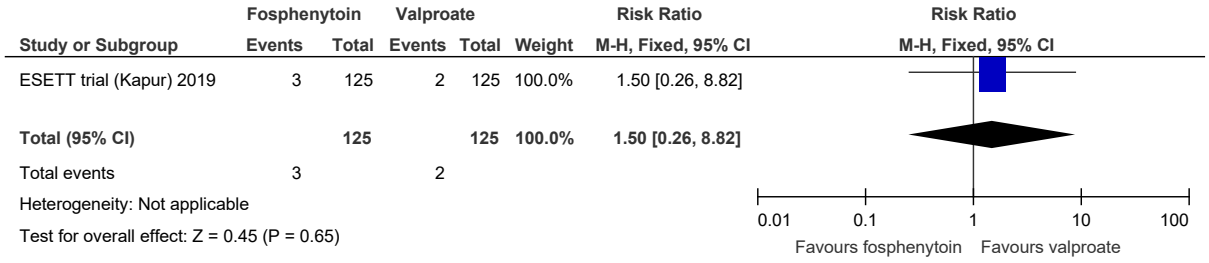
1

Figure 120: Respiratory depression



2 ## E.2.11 Fosphenytoin vs valproate

Figure 121: Mortality



3

Figure 122: Cessation of SE (& improvement in consciousness at 60 min without other anticonvulsant medications)

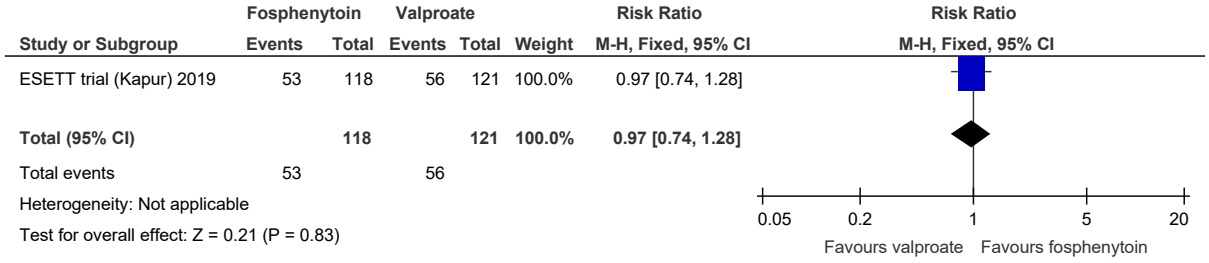


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Figure 123: Seizure recurrence within 24 hours (within 60 min to 12 hours after start of trial drug infusion)

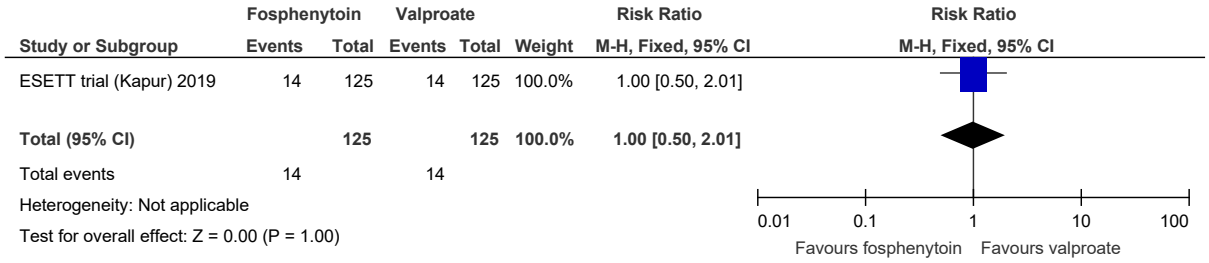


Figure 124: ICU admission

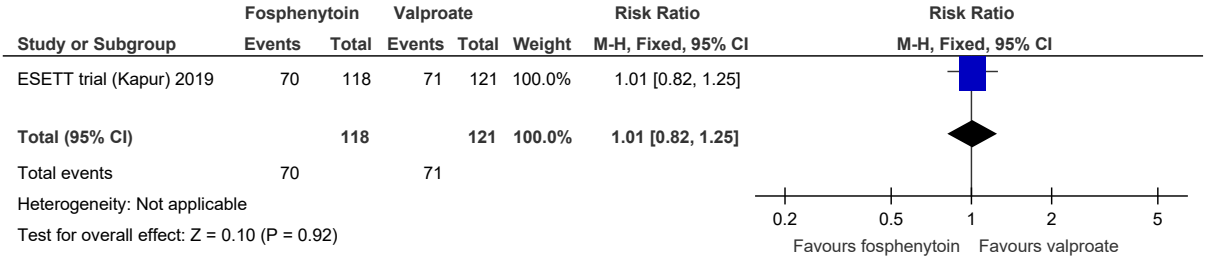


Figure 125: Hypotension (defined as life threatening, within 60 min after start of trial-drug infusion)

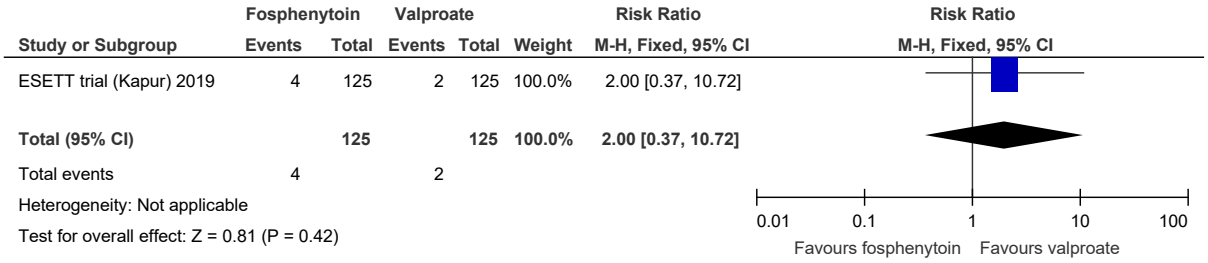
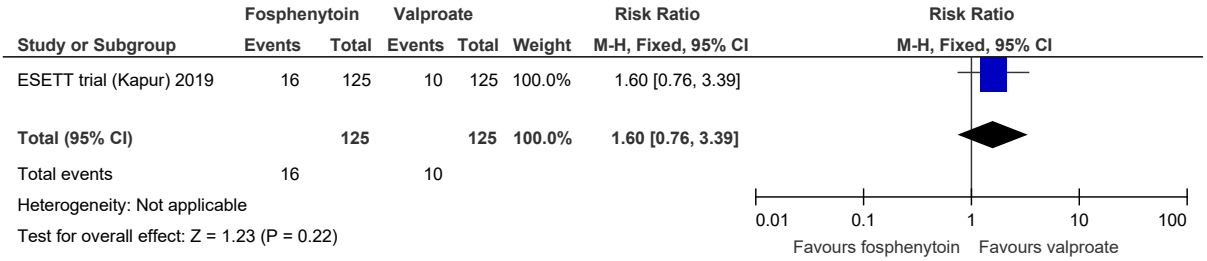


Figure 126: Respiratory depression



Appendix F: GRADE tables

F.1 Monotherapy

Table 28: Clinical evidence profile: Diazepam versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diazepam	Placebo	Relative (95% CI)	Absolute		
Termination of SE at time of arrival at ED												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/68 (42.6%)	15/71 (21.1%)	RR 2.02 (1.19 to 3.42)	215 more per 1000 (from 40 more to 511 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 29: Clinical evidence profile: Diazepam versus drug

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diazepam	Drug	Relative (95% CI)	Absolute		
Mortality - vs lorazepam												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/202 (5.9%)	7/234 (3%)	RR 1.99 (0.8 to 4.95)	30 more per 1000 (from 6 fewer to 118 more)	⊕⊕OO LOW	CRITICAL
Mortality - vs midazolam												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/165 (7.3%)	8/165 (4.8%)	RR 1.5 (0.63 to 3.57)	24 more per 1000 (from 18 fewer to 125 more)	⊕⊕OO LOW	CRITICAL
Termination of SE at time of arrival at ED												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/68 (42.6%)	39/66 (59.1%)	RR 0.72 (0.51 to 1.01)	165 fewer per 1000 (from 290 fewer to 6 more)	⊕⊕OO LOW	CRITICAL
Termination of SE within 5 min - vs midazolam (follow-up 5 min)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	40/49 (81.6%)	49/49 (100%)	RR 0.82 (0.71 to 0.94)	180 fewer per 1000 (from 60 fewer to 290 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Termination of SE within 5 min - vs lorazepam (follow-up 5 min)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	77/202 (38.1%)	65/234 (27.8%)	RR 1.37 (1.05 to 1.8)	103 more per 1000 (from 14 more to 222 more)	⊕⊕OO LOW	CRITICAL
Termination of seizure within 10 min - vs midazolam (follow-up 10 min)												
5	randomised trials	serious[1]	very serious inconsistency[3]	no serious indirectness	serious[2]	none	248/367 (65.4%)	258/347 (74.4%)	RR 0.87 (0.71 to 1.08)	97 fewer per 1000 (from 216 fewer to 59 more)	⊕OOO VERY LOW	CRITICAL
Termination of seizure within 10 min - vs lorazepam (rectal/sublingual) (follow-up 10 min)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	160/202 (79.2%)	131/234 (56%)	RR 1.41 (1.24 to 1.62)	230 more per 1000 (from 134 more to 347 more)	⊕⊕⊕O MODERATE	CRITICAL
Termination of seizure within 10 min - vs lorazepam (IV administration) (follow-up 10 min)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	101/140 (72.1%)	97/133 (72.9%)	RR 0.99 (0.85 to 1.14)	7 fewer per 1000 (from 109 fewer to 102 more)	⊕⊕⊕O MODERATE	CRITICAL
Termination of seizure within 20 min (follow-up 20 min)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	184/202 (91.1%)	194/234 (82.9%)	RR 1.1 (1.02 to 1.18)	83 more per 1000 (from 17 more to 149 more)	⊕⊕⊕O MODERATE	CRITICAL
Time to clinical seizure cessation (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	40	40	-	MD 6.26 lower (20.27 lower to 7.75 higher)	⊕⊕⊕O MODERATE	CRITICAL
Time to cessation after drug administration (Better indicated by lower values)												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	192	168	-	MD 1.45 lower (1.62 to 1.29 lower)	⊕⊕⊕O MODERATE	CRITICAL
Seizure recurrence within 24 hours - vs midazolam (follow-up 24 hours)												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/248 (28.6%)	62/287 (21.6%)	RR 1.34 (1.03 to 1.76)	73 more per 1000 (from 6 more to 164 more)	⊕⊕OO LOW	CRITICAL
Seizure recurrence within 24 hours vs lorazepam (follow-up 24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	119/303 (39.3%)	123/331 (37.2%)	RR 1.06 (0.87 to 1.29)	22 more per 1000 (from 48 fewer to 108 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events, respiratory depression - vs midazolam												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/432 (2.3%)	6/443 (1.4%)	RR 1.67 (0.66 to 4.22)	9 more per 1000 (from 5 fewer to 44 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events, respiratory depression												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	75/202 (37.1%)	54/188 (28.7%)	Peto OR 1.49 (0.95 to 2.34)	80 more per 1000 (from 10 fewer to 170 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse events, hypotension												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/60 (15%)	7/32 (21.9%)	RR 0.69 (0.28 to 1.67)	68 fewer per 1000 (from 157 fewer to 147 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because of heterogeneity I^2=86%, p<0.00001, unexplained by subgroup analysis

Table 30: Clinical evidence profile: Lorazepam versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lorazepam	Placebo	Relative (95% CI)	Absolute		
Mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/66 (7.6%)	11/71 (15.5%)	RR 0.49 (0.18 to 1.33)	79 fewer per 1000 (from 127 fewer to 51 more)	⊕OOO VERY LOW	CRITICAL
Termination of SE at time of arrival at ED												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/66 (59.1%)	15/71 (21.1%)	RR 2.8 (1.71 to 4.58)	380 more per 1000 (from 150 more to 756 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 31: Clinical evidence profile: Lorazepam versus drug

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lorazepam	Drug	Relative (95% CI)	Absolute		
Mortality - vs Diazepam												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/66 (7.6%)	3/68 (4.4%)	RR 1.72 (0.43 to 6.9)	32 more per 1000 (from 25 fewer to 260 more)	⊕OOO VERY LOW	CRITICAL

Mortality - vs Levetiracetam												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/21 (42.9%)	10/23 (43.5%)	RR 0.99 (0.5 to 1.94)	4 fewer per 1000 (from 217 fewer to 409 more)	⊕OOO VERY LOW	CRITICAL
Mortality - vs paraldehyde												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	15/80 (18.8%)	13/80 (16.3%)	RR 1.15 (0.59 to 2.27)	24 more per 1000 (from 67 fewer to 206 more)	⊕⊕OO LOW	CRITICAL
Termination of SE within 10 min - vs diazepam (follow-up 10 min)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/27 (70.4%)	22/34 (64.7%)	RR 1.09 (0.77 to 1.54)	58 more per 1000 (from 149 fewer to 349 more)	⊕⊕OO LOW	CRITICAL
Termination of SE within10 min - vs paraldehyde (follow-up 10 min)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	60/80 (75%)	49/80 (61.3%)	RR 1.22 (0.99 to 1.52)	135 more per 1000 (from 6 fewer to 318 more)	⊕⊕⊕O MODERATE	CRITICAL
Termination of SE at time of arrival at ED - vs diazepam												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39/66 (59.1%)	29/68 (42.6%)	RR 1.39 (0.99 to 1.95)	166 more per 1000 (from 4 fewer to 405 more)	⊕⊕OO LOW	CRITICAL
Termination of SE at time of arrival at ED - vs midazolam												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	282/445 (63.4%)	329/448 (73.4%)	RR 0.86 (0.79 to 0.94)	103 fewer per 1000 (from 44 fewer to 154 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Termination of SE within 30 min (follow-up 30 min)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/41 (75.6%)	29/38 (76.3%)	RR 0.99 (0.77 to 1.27)	8 fewer per 1000 (from 176 fewer to 206 more)	⊕⊕OO LOW	CRITICAL
Time to seizure cessation (Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 1.57 lower (12.44 lower to 9.3 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Seizure recurrence within 24 hours - vs Diazepam (follow-up 24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/27 (22.2%)	12/34 (35.3%)	RR 0.63 (0.27 to 1.46)	131 fewer per 1000 (from 258 fewer to 162 more)	⊕OOO VERY LOW	CRITICAL
Seizure recurrence within 24 hours - vs Levetiracetam (follow-up 24 hours)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/41 (24.4%)	6/38 (15.8%)	RR 1.54 (0.62 to 3.84)	85 more per 1000 (from 60 fewer to 448 more)	⊕OOO VERY LOW	CRITICAL
Seizure recurrence within 24 hours - vs midazolam (follow-up 24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	47/445 (10.6%)	51/448 (11.4%)	RR 0.93 (0.64 to 1.35)	8 fewer per 1000 (from 41 fewer to 40 more)	⊕OOO VERY LOW	CRITICAL
Seizure recurrence within 24 hours - vs paraldehyde (follow-up 24 hours)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/80 (10%)	11/80 (13.8%)	RR 0.73 (0.31 to 1.71)	37 fewer per 1000 (from 95 fewer to 98 more)	⊕⊕OO LOW	CRITICAL
Seizure freedom at 24 hours (follow-up 24 hours)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/41 (51.2%)	23/38 (60.5%)	RR 0.85 (0.57 to 1.25)	91 fewer per 1000 (from 260 fewer to 151 more)	⊕OOO VERY LOW	CRITICAL
Length of hospital stay (days) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	285	251	-	MD 1.2 lower (2.64 lower to 0.24 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Length of ICU stay (days) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	155	123	-	MD 1.6 lower (3.43 lower to 0.23 higher)	⊕⊕⊕O MODERATE	IMPORTANT

Adverse events, respiratory failure - Lorazepam vs Levetiracetam											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/21 (47.6%)	5/23 (21.7%)	RR 2.19 (0.89 to 5.37)	259 more per 1000 (from 24 fewer to 950 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events, hypotension - vs diazepam											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/27 (3.7%)	7/34 (20.6%)	RR 0.18 (0.02 to 1.37)	169 fewer per 1000 (from 202 fewer to 76 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events, hypotension - vs Levetiracetam											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/21 (38.1%)	2/23 (8.7%)	RR 4.38 (1.05 to 18.35)	294 more per 1000 (from 4 more to 1000 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events, hypotension - vs Phenobarbital											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48/136 (35.3%)	57/124 (46%)	RR 0.77 (0.57 to 1.03)	106 fewer per 1000 (from 198 fewer to 14 more)	⊕⊕OO LOW	IMPORTANT
Adverse events, hypotension - vs Phenytoin											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48/136 (35.3%)	42/127 (33.1%)	RR 1.07 (0.76 to 1.49)	23 more per 1000 (from 79 fewer to 162 more)	⊕⊕OO LOW	IMPORTANT
Adverse events, hypotension - vs midazolam											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/445 (2.9%)	12/448 (2.7%)	RR 1.09 (0.5 to 2.36)	2 more per 1000 (from 13 fewer to 36 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 32: Clinical evidence profile: Valproate versus drug

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Drug	Relative (95% CI)	Absolute		
Termination of SE after drug infusion												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/35 (65.7%)	14/33 (42.4%)	RR 1.55 (0.97 to 2.46)	233 more per 1000 (from 13 fewer to 619 more)	⊕⊕OO LOW	CRITICAL
Seizure recurrence within 24 hours (follow-up 24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6/35 (17.1%)	13/33 (39.4%)	RR 0.44 (0.19 to 1.01)	221 fewer per 1000 (from 319 fewer to 4 more)	⊕⊕OO LOW	CRITICAL
Seizure freedom at 24 hours (follow-up 24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/35 (22.9%)	10/33 (30.3%)	RR 0.75 (0.34 to 1.68)	76 fewer per 1000 (from 200 fewer to 206 more)	⊕OOO VERY LOW	CRITICAL
Adverse events, Respiratory depression												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/23 (4.3%)	2/14 (14.3%)	RR 0.3 (0.03 to 3.06)	100 fewer per 1000 (from 139 fewer to 294 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 33: Clinical evidence profile: Phenytoin versus phenobarbital

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenytoin	Phenobarbital	Relative (95% CI)	Absolute		
Adverse events, hypotension												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42/127 (33.1%)	57/124 (46%)	RR 0.72 (0.53 to 0.98)	129 fewer per 1000 (from 9 fewer to 216 fewer)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

F.2 Add on therapies

Table 34: Clinical evidence profile: sodium valproate versus phenytoin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Phenytoin	Relative (95% CI)	Absolute		
Mortality												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/140 (8.6%)	11/140 (7.9%)	RR 1.09 (0.51 to 2.32)	7 more per 1000 (from 39 fewer to 104 more)	⊕OOO VERY LOW	CRITICAL
Cessation of SE within 15 minutes												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	29/35 (82.9%)	31/35 (88.6%)	RR 0.94 (0.77 to 1.13)	53 fewer per 1000 (from 204 fewer to 115 more)	⊕⊕⊕O MODERATE	CRITICAL
Cessation of SE within 20 min												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/50 (88%)	42/50 (84%)	RR 1.05 (0.89 to 1.23)	42 more per 1000 (from 92 fewer to 193 more)	⊕⊕⊕O MODERATE	CRITICAL
Cessation of SE within 12 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/15 (73.3%)	9/15 (60%)	RR 1.22 (0.73 to 2.04)	132 more per 1000 (from 162 fewer to 624 more)	⊕OOO VERY LOW	CRITICAL
Cessation of SE within 7 days												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	43/55 (78.2%)	39/55 (70.9%)	RR 1.1 (0.89 to 1.37)	71 more per 1000 (from 78 fewer to 262 more)	⊕⊕OO LOW	CRITICAL
Time to seizure cessation (minutes) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	35	35	-	MD 0.20 lower (0.81 lower to 0.41 higher)	⊕⊕⊕O MODERATE	CRITICAL
Seizure recurrence within 24 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/50 (12%)	8/50 (16%)	RR 0.75 (0.28 to 2)	40 fewer per 1000 (from 115 fewer to 160 more)	⊕OOO VERY LOW	CRITICAL
PICU admission (days) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	35	35	-	MD 6.0 higher (4.31 to 7.69 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Length of stay (days) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	35	35	-	MD 0.60 lower (2.85 lower to 1.65 higher)	⊕⊕OO LOW	CRITICAL
Hypotension												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/105 (0%)	9/105 (8.6%)	Peto OR 0.12 (0.03 to 0.47)	90 fewer per 1000 (from 140 fewer to 30 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Respiratory depression												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/50 (0%)	2/50 (4%)	Peto OR 0.13 (0.01 to 2.15)	40 fewer per 1000 (from 110 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[3] Downgraded by 2 increment as the confidence interval crossed 2 default MIDs of -0.27 and 0.27

1

2 **Table 35: Clinical evidence profile: Levetiracetam versus phenytoin**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	Phenytoin	Relative (95% CI)	Absolute		
Mortality												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/346 (1.4%)	7/335 (2.1%)	Peto OR 0.78 (0.24 to 2.52)	0 fewer per 1000 (from 30 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
Cessation of SE within 5 min												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	94/171 (55%)	104/166 (62.7%)	RR 0.88 (0.74 to 1.05)	75 fewer per 1000 (from 163 fewer to 31 more)	⊕⊕OO LOW	CRITICAL
Cessation of SE within 5 - 20 minutes												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	17/52 (32.7%)	15/52 (28.8%)	RR 1.13 (0.64 to 2.02)	37 more per 1000 (from 104 fewer to 294 more)	⊕OOO VERY LOW	CRITICAL
Cessation of SE within 15 minutes												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/32 (93.8%)	31/35 (88.6%)	RR 1.06 (0.91 to 1.23)	53 more per 1000 (from 80 fewer to 204 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Cessation of SE within 20 - 40 minutes												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/52 (1.9%)	1/52 (1.9%)	RR 1 (0.06 to 15.57)	0 fewer per 1000 (from 18 fewer to 280 more)	⊕OOO VERY LOW	CRITICAL
Cessation of SE within 30 min												

2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	291/322 (90.4%)	265/322 (82.3%)	RR 1.10 (1.03 to 1.17)	82 more per 1000 (from 25 more to 140 more)	⊕⊕OO LOW	CRITICAL
Cessation of SE within 2 h												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	61/119 (51.3%)	62/114 (54.4%)	RR 0.94 (0.74 to 1.2)	33 fewer per 1000 (from 141 fewer to 109 more)	⊕⊕⊕O MODERATE	CRITICAL
Cessation of SE within 24 h												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18/22 (81.8%)	21/30 (70%)	RR 1.17 (0.86 to 1.59)	119 more per 1000 (from 98 fewer to 413 more)	⊕⊕⊕O MODERATE	CRITICAL
Recurrence of seizure within 24 h												
2	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[1]	none	11/74 (14.9%)	24/74 (32.4%)	RR 0.46 (0.24 to 0.87)	175 fewer per 1000 (from 42 fewer to 246 fewer)	⊕OOO VERY LOW	CRITICAL
Time to seizure cessation (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32	35	-	MD 0.10 higher (0.5 lower to 0.7 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean duration of SE of good responders (Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	13	15	-	MD 2.2 higher (19.36 lower to 23.76 higher)	⊕OOO VERY LOW	CRITICAL
Good outcome at discharge (FIM score)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	19/22 (86.4%)	18/22 (81.8%)	RR 1.06 (0.82 to 1.37)	49 more per 1000 (from 147 fewer to 303 more)	⊕⊕OO LOW	CRITICAL
Good outcome at discharge (mRS score)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/22 (54.5%)	12/30 (40%)	RR 1.36 (0.76 to 2.44)	144 more per 1000 (from 96 fewer to 576 more)	⊕⊕OO LOW	CRITICAL

Mean length of hospital stay (days) (Better indicated by lower values)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	57	-	MD 0.29 higher (0.46 lower to 1.05 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean length of PICU admission (days) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32	35	-	MD 2.0 higher (0.49 to 3.51 higher)	⊕⊕⊕O MODERATE	CRITICAL
Admission to critical care												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	97/152 (63.8%)	72/134 (53.7%)	RR 1.19 (0.97 to 1.45)	102 more per 1000 (from 16 fewer to 242 more)	⊕⊕OO LOW	CRITICAL
Hypotension												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	3/154 (1.9%)	5/160 (3.1%)	RR 0.67 (0.16 to 2.73)	10 fewer per 1000 (from 26 fewer to 54 more)	⊕OOO VERY LOW	CRITICAL
Adverse events, confusion												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/132 (0.76%)	0/130 (0%)	OR 7.28 (0.14 to 366.83)	10 more per 1000 (from 10 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
Cardiac Depression												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	0/300 (0%)	2/300 (0.67%)	Peto 0.13 (0.01 to 2.16)	6 fewer per 1000 (from 7 fewer to 8 more)	⊕OOO VERY LOW	CRITICAL
Respiratory Depression												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	0/300 (0%)	6/300 (2%)	RR 0.08 (0 to 1.36)	18 fewer per 1000 (from 20 fewer to 7 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[3] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Table 36: Clinical evidence profile: Lignocaine versus midazolam

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lignocaine	Midazolam	Relative (95% CI)	Absolute		
Cessation of SE												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/10 (50%)	2/10 (20%)	RR 2.5 (0.63 to 10)	300 more per 1000 (from 74 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Length of ICU stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 4.6 lower (8.4 to 0.8 lower)	⊕⊕⊕O MODERATE	CRITICAL
Intubation needing mechanical ventilation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/10 (20%)	7/10 (70%)	RR 0.29 (0.08 to 1.05)	497 fewer per 1000 (from 644 fewer to 35 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 37: Clinical evidence profile: Valproate versus lacosamide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Lacosamide	Relative (95% CI)	Absolute		

Mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/33 (36.4%)	10/33 (30.3%)	RR 1.2 (0.6 to 2.38)	61 more per 1000 (from 121 fewer to 418 more)	⊕OOO VERY LOW	CRITICAL
Time for seizure cessation after drug administration (min) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	33	-	MD 0.61 lower (1.81 lower to 0.59 higher)	⊕⊕OO LOW	CRITICAL
Cessation of SE for 1 hour												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	23/33 (69.7%)	21/33 (63.6%)	RR 1.1 (0.78 to 1.54)	64 more per 1000 (from 140 fewer to 344 more)	⊕OOO VERY LOW	CRITICAL
Seizure freedom within 24 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/33 (60.6%)	15/33 (45.5%)	RR 1.33 (0.84 to 2.12)	150 more per 1000 (from 73 fewer to 509 more)	⊕⊕OO LOW	CRITICAL
Hypotension												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/33 (0%)	1/33 (3%)	Peto OR 0.14 (0 to 6.82)	30 fewer per 1000 (from 110 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 38: Clinical evidence profile: Midazolam versus diazepam

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Midazolam**	**Diazepam**	**Relative (95% CI)**	**Absolute**		
Mortality												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/21 (38.1%)	2/19 (10.5%)	RR 3.62 (0.87 to 14.97)	276 more per 1000 (from 14 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Time to initial seizure cessation (min) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	19	-	MD 0.1 higher (7.04 lower to 7.24 higher)	⊕⊕⊕O MODERATE	CRITICAL
Time to final seizure cessation (min) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	19	-	MD 81 higher (25.04 lower to 187.04 higher)	⊕⊕⊕O MODERATE	
Cessation of SE within 12 hours (6 hours)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18/21 (85.7%)	17/19 (89.5%)	RR 0.96 (0.76 to 1.21)	36 fewer per 1000 (from 215 fewer to 188 more)	⊕⊕⊕O MODERATE	CRITICAL
Seizure recurrence whilst on infusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	12/21 (57.1%)	3/19 (15.8%)	RR 3.62 (1.2 to 10.9)	414 more per 1000 (from 32 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Seizure recurrence after stopping infusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/21 (19%)	3/19 (15.8%)	RR 1.21 (0.31 to 4.71)	33 more per 1000 (from 109 fewer to 586 more)	⊕⊕OO LOW	CRITICAL
Hypotension												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/21 (38.1%)	9/19 (47.4%)	RR 0.8 (0.39 to 1.66)	95 fewer per 1000 (from 289 fewer to 313 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 39: Clinical evidence profile: Propofol versus midazolam

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propofol	Midazolam	Relative (95% CI)	Absolute		
Mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/11 (72.7%)	7/12 (58.3%)	RR 1.25 (0.68 to 2.27)	146 more per 1000 (from 187 fewer to 741 more)	⊕OOO VERY LOW	CRITICAL
Cessation of SE for 48 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/11 (45.5%)	3/12 (25%)	RR 1.82 (0.56 to 5.88)	205 more per 1000 (from 110 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Hypotension												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/11 (27.3%)	1/12 (8.3%)	RR 3.27 (0.4 to 27)	189 more per 1000 (from 50 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 40: Clinical evidence profile: Phenobarbital versus valproate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenobarbital	Valproate	Relative (95% CI)	Absolute		
Mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/37 (16.2%)	11/36 (30.6%)	RR 0.53 (0.22 to 1.28)	144 fewer per 1000 (from 238 fewer to 86 more)	⊕OOO VERY LOW	CRITICAL
Seizure control within 20 min												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/30 (76.7%)	27/30 (90%)	RR 0.85 (0.68 to 1.07)	135 fewer per 1000 (from 288 fewer to 63 more)	⊕⊕OO LOW	CRITICAL
Recurrence of seizure within 24 hours: Children												
1	randomised trials	serious[1]	no serious inconsistency[3]	no serious indirectness	no serious imprecision[2]	none	12/23 (52.2%)	4/27 (14.8%)	RR 3.52 (1.31 to 9.44)	373 more per 1000 (from 46 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Recurrence of seizure within 24 hours: Adults												
2	randomised trials	serious[1]	no serious inconsistency[3]	no serious indirectness	serious[2]	none	2/30 (6.7%)	5/16 (31.3%)	RR 0.21 (0.05 to 0.98)	247 fewer per 1000 (from 6 fewer to 297 fewer)	⊕⊕OO LOW	CRITICAL
Hypotension: Children												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	1/30 (3.3%)	Peto OR 0.14 (0 to 6.82)	29 fewer per 1000 (from 33 fewer to 157 more)	⊕OOO VERY LOW	CRITICAL
Hypotension: Adults												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/30 (6.7%)	5/16 (31.3%)	Peto OR 0.16 (0.32 to 0.82)	245 fewer per 1000 (from 41 fewer to 186 fewer)	⊕⊕OO LOW	CRITICAL
Transient depressed respiration												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	7/67 (10.4%)	0/66 (0%)	Peto OR 8.18 (1.78 to 37.71)	100 more per 1000 (from 20 more to 190 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because the confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis.

Table 41: Clinical evidence profile: Sodium valproate versus diazepam

Quality assessment						No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Diazepam	Relative (95% CI)	Absolute		
Mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/30 (16.7%)	2/35 (5.7%)	RR 2.92 (0.61 to 13.96)	110 more per 1000 (from 22 fewer to 741 more)	⊕⊕OO LOW	CRITICAL
Cessation of SE within 30 min												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	16/20 (80%)	17/20 (85%)	RR 0.94 (0.71 to 1.25)	51 fewer per 1000 (from 247 fewer to 213 more)	⊕⊕⊕O MODERATE	CRITICAL
Cessation of SE within 1 hour												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	15/30 (50%)	20/36 (55.6%)	RR 0.9 (0.57 to 1.43)	56 fewer per 1000 (from 239 fewer to 239 more)	⊕⊕OO LOW	CRITICAL
Time for seizure cessation after drug administration (min) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20	20	-	MD 17.8 lower (29.94 to 5.66 lower)	⊕⊕⊕O MODERATE	CRITICAL
Recurrence of seizure within 24 hours												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/15 (20%)	5/20 (25%)	RR 0.8 (0.23 to 2.83)	50 fewer per 1000 (from 192 fewer to 457 more)	⊕⊕OO LOW	CRITICAL
ICU admission												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11/20 (55%)	19/20 (95%)	RR 0.58 (0.38 to 0.87)	399 fewer per 1000 (from 123 fewer to 589 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Hypotension												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/50 (0%)	12/56 (21.4%)	Peto OR 0.09 (0.02 to 0.3)	220 fewer per 1000 (from 330 fewer to 120 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Respiratory depression												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/20 (0%)	12/20 (60%)	Peto OR 0.06 (0.02 to 0.23)	600 fewer per 1000 (from 820 fewer to 380 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Need for intubation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/30 (0%)	2/36 (5.6%)	Peto OR 0.16 (0.01 to 2.57)	60 fewer per 1000 (from 150 fewer to 40 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 42: Clinical evidence profile: Levetiracetam versus Fosphenytoin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Levetiracetam**	**Fosphenytoin**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/150 (4.7%)	3/125 (2.4%)	RR 1.94 (0.51 to 7.36)	23 more per 1000 (from 12 fewer to 153 more)	⊕OOO VERY LOW	CRITICAL
Cessation of SE from 10 - 20 minutes												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	53/58 (91.4%)	54/58 (93.1%)	RR 0.98 (0.88 to 1.09)	19 fewer per 1000 (from 112 fewer to 84 more)	⊕⊕OO LOW	CRITICAL
Cessation of seizure within 5 minutes												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/25 (92%)	21/25 (84%)	RR 1.10 (0.89 to 1.35)	84 more per 1000 (from 92 fewer to 294 more)	⊕⊕OO LOW	CRITICAL
Cessation of SE (and improvement in consciousness at 60 min without other anticonvulsant medications) (follow-up 60 minutes)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	68/145 (46.9%)	53/118 (44.9%)	RR 1.04 (0.8 to 1.36)	18 more per 1000 (from 90 fewer to 162 more)	⊕⊕OO LOW	CRITICAL
Time to seizure cessation (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 0.80 higher (0.09 to 1.51 higher)	⊕⊕OO LOW	CRITICAL
Seizure recurrence within 24 hours (within 60 mins to 12 hours after start of trial drug infusion) (follow-up 60 mins to 12 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	21/175 (12%)	17/150 (11.3%)	RR 1.07 (0.59 to 1.95)	8 more per 1000 (from 46 fewer to 108 more)	⊕OOO VERY LOW	CRITICAL
Seizure recurrence within 48 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/58 (17.2%)	13/58 (22.4%)	RR 0.77 (0.37 to 1.61)	52 fewer per 1000 (from 141 fewer to 137 more)	⊕OOO VERY LOW	CRITICAL
Length of hospital stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 0.50 higher (1.91 lower to 2.91 higher)	⊕⊕OO LOW	CRITICAL
Length of PICU stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 1.70 higher (25.88 lower to 29.28 higher)	⊕⊕⊕O MODERATE	CRITICAL
ICU admission (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87/145 (60%)	70/118 (59.3%)	RR 1.01 (0.83 to 1.25)	6 more per 1000 (from 101 fewer to 148 more)	⊕⊕⊕O MODERATE	CRITICAL
Hypotension (defined as life threatening, within 60 mins after start of trial-drug infusion) (follow-up 60 minutes)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/150 (0.67%)	4/125 (3.2%)	RR 0.21 (0.02 to 1.84)	25 fewer per 1000 (from 31 fewer to 27 more)	⊕OOO VERY LOW	CRITICAL
Respiratory depression												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/175 (6.9%)	18/150 (12%)	RR 0.57 (0.29 to 1.14)	52 fewer per 1000 (from 85 fewer to 17 more)	⊕⊕OO LOW	IMPORTANT
Bradycardia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/58 (0%)	1/58 (1.7%)	Peto 0.14 (0.00 to 6.82)	15 fewer per 1000 (from 17 fewer to 100 more)	⊕OOO VERY LOW	CRITICAL
Tracheal Intubation												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/58 (1.7%)	3/58 (5.2%)	RR 0.33 (0.04 to 3.11)	35 fewer per 1000 (from 50 fewer to 109 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 43: Clinical evidence profile: Levetiracetam versus valproate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Levetiracetam**	**Valproate**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up 30 days)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	7/182 (3.8%)	3/160 (1.9%)	RR 1.94 (0.53 to 7.1)	18 more per 1000 (from 9 fewer to 114 more)	⊕OOO VERY LOW	CRITICAL
Cessation of SE within 15 minutes												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	30/32 (93.8%)	29/35 (82.9%)	RR 1.13 (0.95 to 1.35)	108 more per 1000 (from 41 fewer to 290 more)	⊕⊕⊕O MODERATE	CRITICAL
Time to seizure cessation (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	32	35	-	MD 0.10 lower (0.75 lower to 0.55 higher)	⊕⊕⊕O MODERATE	CRITICAL
Cessation of SE (and improvement in consciousness at 60 min without other anticonvulsant medications) (follow-up 60 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	68/145 (46.9%)	53/118 (44.9%)	RR 1.04 (0.8 to 1.36)	18 more per 1000 (from 90 fewer to 162 more)	⊕⊕OO LOW	CRITICAL
Seizure recurrence within 24 hours (within 60 mins to 12 hours after start of trial drug infusion) (follow-up 60 mins to 12 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/150 (10.7%)	14/125 (11.2%)	RR 0.95 (0.48 to 1.87)	6 fewer per 1000 (from 58 fewer to 97 more)	⊕OOO VERY LOW	CRITICAL
Length of hospital stay (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	32	35	-	MD 1.50 higher (1.63 lower to 4.63 higher)	⊕⊕⊕O MODERATE	CRITICAL
Length of PICU admission (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	32	35	-	MD 4.0 lower (5.97 to 2.03 lower)	⊕⊕⊕O MODERATE	CRITICAL
ICU admission												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87/145 (60%)	71/121 (58.7%)	RR 1.02 (0.84 to 1.25)	12 more per 1000 (from 94 fewer to 147 more)	⊕⊕⊕O MODERATE	CRITICAL
Hypotension (defined as life threatening, within 60 mins after start of trial-drug infusion) (follow-up 60 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/150 (0.67%)	2/125 (1.6%)	RR 0.42 (0.04 to 4.54)	9 fewer per 1000 (from 15 fewer to 57 more)	⊕OOO VERY LOW	CRITICAL

Respiratory depression												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/150 (8%)	10/125 (8%)	RR 1.00 (0.45 to 2.24)	0 fewer per 1000 (from 44 fewer to 99 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, unexplained by subgroup analysis. The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 44: Clinical evidence profile: Fosphenytoin versus valproate

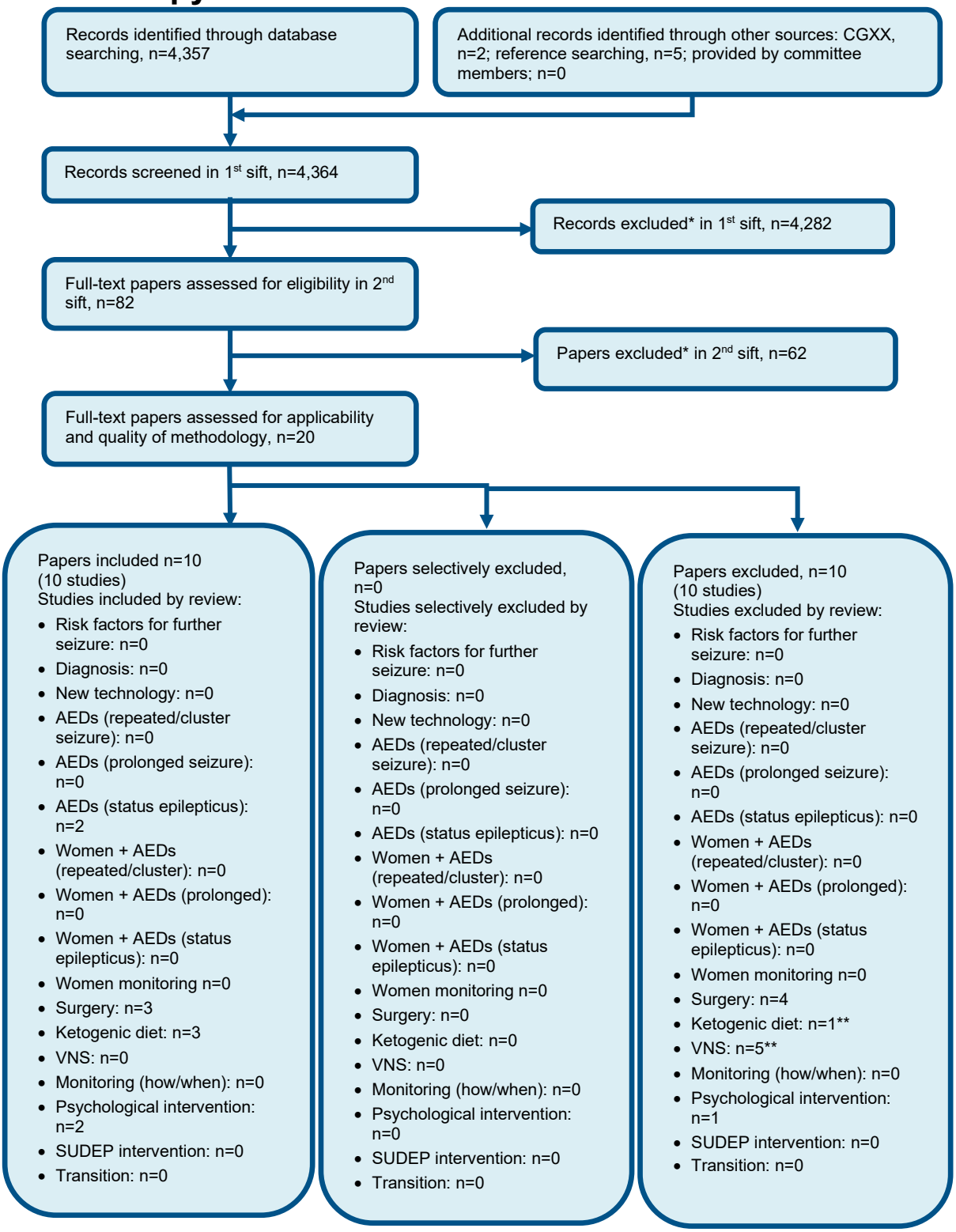
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fosphenytoin**	**Valproate**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious	none	3/125 (2.4%)	2/125 (1.6%)	RR 1.50 (0.26 to 8.82)	8 more per 1000 (from 12 fewer to 125 more)	⊕OOO VERY LOW	CRITICAL
Cessation of SE (and improvement in consciousness at 60 min without other anticonvulsant medications) (follow-up 60 min)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	53/118 (44.9%)	56/121 (46.3%)	RR 0.97 (0.74 to 1.28)	14 fewer per 1000 (from 120 fewer to 130 more)	⊕⊕OO LOW	CRITICAL
Seizure recurrence within 24 hours (within 60 min to 12 hours after start of trial drug infusion) (follow-up 60 min to 12 hours)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	14/125 (11.2%)	14/125 (11.2%)	RR 1.00 (0.50 to 2.01)	0 fewer per 1000 (from 56 fewer to 113 more)	⊕OOO VERY LOW	CRITICAL
ICU admission												

1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	70/118 (59.3%)	71/121 (58.7%)	RR 1.01 (0.82 to 1.25)	6 more per 1000 (from 106 fewer to 147 more)	⊕⊕⊕O MODERATE	CRITICAL
Hypotension (defined as life threatening, within 60 min after start of trial-drug infusion) (follow-up 60 min)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	4/125 (3.2%)	2/125 (1.6%)	RR 2.00 (0.37 to 10.72)	16 more per 1000 (from 10 fewer to 156 more)	⊕OOO VERY LOW	CRITICAL
Respiratory depression												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	16/125 (12.8%)	10/125 (8%)	RR 1.60 (0.76 to 3.39)	48 more per 1000 (from 19 fewer to 191 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

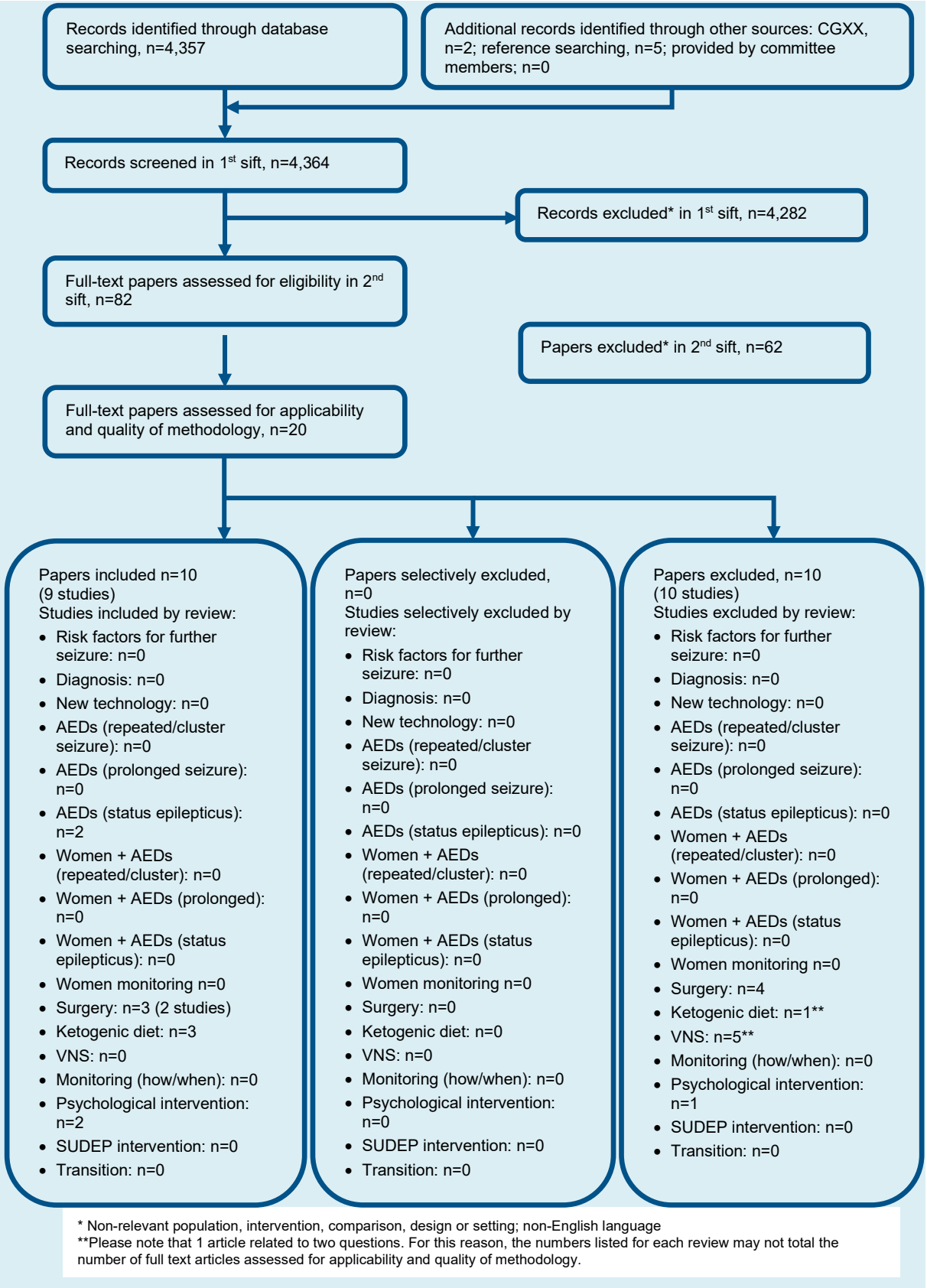
Appendix G: Health economic evidence selection

G.1 Monotherapy



* Non-relevant population, intervention, comparison, design or setting; non-English language
**Please note that 1 article related to two questions. For this reason, the numbers listed for each review may not total the number of full text articles assessed for applicability and quality of methodology.

G.2 Add on Therapy



Appendix H: Health economic evidence tables

H.1 Monotherapy

Study	Lee 2013 [91]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** A discrete event simulation model followed by a decision tree, which estimated the clinical outcomes associated with prolonged, acute, convulsive seizures occurring in the community setting, and captured the associated resource use and health related quality of life implications. Costs were attached to resource use and combined with QALYs to determine cost effectiveness.	**Population:** Paediatric patients with a diagnosis of epilepsy suffering prolonged, acute, convulsive seizures in the community setting. **Cohort settings:** Start age: Not reported Male: Not reported **Intervention 1:** Standard care (95% buccal Midazolam, 5% rectal Diazepam) **Intervention 2:** Buccolam (dose is one syringe (a pack = 4 syringes)) **Intervention 3:** Buccal Midazolam (4 doses per bottle)	**Total costs (mean per patient):** Intervention 1: £23,070 Intervention 2: £20,130 Intervention 3: £21,016 Intervention 4: £34,399 Incremental (2−1): -£2,939 (95% CI: NR; p=NR) Incremental (2−3): -£886 (95% CI: NR; p=NR) Incremental (2−4): -£14,269 (95% CI: NR; p=NR) **Currency & cost year:** 2012-13 UK pounds **Cost components incorporated:** Drug costs, ambulance costs, hospital costs	**QALYs (mean per patient):** Intervention 1: 3.738 Intervention 2: 3.763 Intervention 3: 3.749 Intervention 4: 3.681 Incremental (2−1): 0.025 (95% CI: NR; p=NR) Incremental (2−3): 0.013 (95% CI: NR; p=NR) Incremental (2−4): 0.082 (95% CI: NR; p=NR)	**ICER:** Intervention 2 dominates all other interventions. (pa) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR **Analysis of uncertainty:** Probabilistic sensitivity analysis was performed with 10,000 Monte Carlo simulations. Scenario analyses undertaken include: • Unlicensed buccal Midazolam has shelf life of 3 months when opened in all locations (base case was 24 months) • Each bottle of unlicensed buccal Midazolam has 6 doses instead of 4. • Two bottles of unlicensed buccal Midazolam ordered per prescription (instead of 1) which lowers the cost slightly) • Buccolam and unlicensed buccal Midazolam are as effective as diazepam rather than more effective. All showed that Buccolam would still be cost saving.

Perspective: UK NHS (Wales) **Time horizon/Follow-up:** 6 years **Treatment effect duration:**[(a)] 30 days [(b)] **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 4:** Rectal Diazepam (dose not stated)	(inpatient admissions and ICU/HDU admissions)		• A threshold analysis varying the cost of Buccolam until Buccolam is no longer cost saving. • A 1-year time horizon was also tested.
Data sources				
Model structure: A discrete event simulation that estimated the frequency and location of occurrence of seizures, and a decision tree that assessed the treatment pathway when a child had a seizure. By estimating the frequency and location of prolonged seizures the discrete event simulation enabled the estimate of drug wastage and the probability that rescue medication was not present which then enabled the decision tree to calculate the costs and health consequences following the seizure. The discrete event simulation simulated 5000 patients for each treatment. For each of these patients, the frequency, location of seizures and the initial store of drugs at each location were simulated at the start of the model. The availability of medication at each location was then adjusted by the occurrence of seizures within the model time horizon. If the model reached a point where drugs were disposed of due to expiry, then the value of the disposed products were calculated, and new products ordered as replacements. The decision tree had the following possible chance nodes: whether medication was available; if treatment was administered by parent/caregiver and if it was successful; if seizure lasted >10 mins if treatment was given; whether care plan recommended giving second dose if seizure lasted > 10 mins; whether child had repeat seizure if seizure lasted >10 mins; if an ambulance was called and whether: ambulance could administer treatment; whether patient was taken to hospital and if they were admitted; if they were admitted then whether they were admitted to intensive care, and other inputs like the assumptions behind wastage. A time horizon of 6 years was used because this is the shortest period for which the shelf life of Buccolam (18 months) and buccal midazolam (24 months) coincide. **Health outcomes:** Probability of further seizure and of seizure cessation taken from McIntyre et al 2005[115] which was a UK randomised study. Two surveys were undertaken to find other model inputs: a survey of parents with children with epilepsy, and a Delphi panel audit of clinicians. The survey of parents was used to determine the frequency, location of occurrences and average length of seizures, and other descriptive aspects of epilepsy. Nineteen responses were gathered from Wales with a similar survey conducted in Scotland that received 43 responses and had similar results and was also used. The Delphi used 5 clinical experts, and this informed probabilities such as a failed delivery, and patients being admitted. **Quality-of-life weights:** Clinicians asked to value health states on behalf of patients using the EQ-5D, by estimating the QoL during and shortly after a seizure. The clinicians estimated that 20% of children would be cognitively impaired and would have a lower baseline QoL so also estimated utility decrements from seizures of different levels of severity for cognitively impaired children also. **Cost sources:** Cost of buccal Midazolam also includes a £20 sourcing fee per prescription because it was unlicensed at the time of the analysis. Drug costs from BNF. Cost of hospital admission and ambulance callouts from NHS reference costs 2011-12. Includes estimation of drug wastage, because Buccal midazolam is supplied in bottles containing multiple doses, so it cannot be spread across possible locations and much of the product is not used before expiry leading to wastage, whereas Buccolam comes in separate doses. Where the product expired before all of it is used then the remaining cost of the product is calculated, and new product ordered but assumed that where all the product has been used there would be no further wastage at that location for the rest of the model.				
Comments				

Source of funding: ViroPharma (manufacturers of Buccolam). **Limitations:** UK study (Wales), EQ-5D but filled in by clinicians not patients or their parents/carers. Costs out of date: Buccal Midazolam in particular based on current BNF costs this would be more expensive now because only comes in one pre-filled syringe. But costs depend on dose and how it is packaged (separate pre-filled multiple syringes or not) so uncertainty about cost effectiveness based on which buccal product is used as there are generic versions available which are not listed in the BNF. Funded by manufacturers. Most inputs elicited from surveys and are assumptions. **Other:**

Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Note that the treatment effect duration is 30 days because that is the length of the cycles in the model with a disutility being attached to the seizure for this period of time before returning to baseline.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Lee 2014** [92]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Deterministic decision analytic model **Approach to analysis:** A discrete event simulation model followed by a decision tree, which estimated the clinical outcomes associated with prolonged, acute, convulsive seizures occurring in the community setting, and captured the associated resource use and health related quality of	**Population:** Paediatric patients with a diagnosis of epilepsy suffering prolonged, acute, convulsive seizures in the community setting. **Cohort settings:** Start age: Not reported Male: Not reported **Intervention 1:** Standard care (varies dependent on the perspective)	**Total costs (mean per patient) (Scottish perspective):** Intervention 1: £4,472 Intervention 2: £4,150 Intervention 3: £4,472 Intervention 4: £5,644 Incremental (2−1): -£322 (95% CI: NR; p=NR) Incremental (2−3): -£322 *(same as above because in the Scottish perspective standard care in the community is 100% buccal midazolam)*	**QALYs (mean per patient) (Scottish perspective):** Intervention 1: 0.75030 Intervention 2: 0.75112 Intervention 3: 0.75030 Intervention 4: 0.74475 Incremental (2−1): 0.00082 (95% CI: NR; p=NR) Incremental (2−3): 0.00082 (95% CI: NR; p=NR) Incremental (2−4): 0.00637 (95% CI: NR; p=NR)	**ICER:** Intervention 2 dominates all other interventions. 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR **Analysis of uncertainty:** Unclear if there was a probabilistic sensitivity analysis. Upper and lower bounds of each parameter used in deterministic sensitivity analysis. The three most influential parameters on the results for the Scottish perspective were: • Probability carer doesn't administer treatment with buccal midazolam.

life implications. Costs were attached to resource use and combined with QALYs to determine cost effectiveness. *Note that 7 different country perspectives are modelled, but only Scotland is extracted here because the Wales perspective is included in the paper above, and the Scottish and Welsh perspectives are assumed to be closest to that of England.* **Perspective:** Scotland NHS **Time horizon/Follow-up:** 1 year **Treatment effect duration:**[(a)] Length of seizures **Discounting:** Costs: NA; Outcomes: NA	**Intervention 2:** Buccolam (dose is one syringe (a pack = 4 syringes))* **Intervention 3:** Buccal Midazolam (4 doses per bottle)* **Intervention 4:** Rectal Diazepam (dose not stated) *assumed based on methods of other Lee paper	(95% CI: NR; p=NR) Incremental (2−4): -£1,494 (95% CI: NR; p=NR) **Currency & cost year:** 2012 Euros converted to 2012 UK pounds. **Cost components incorporated:** Drug costs, ambulance costs, hospital costs (inpatient admissions and ICU/HDU admissions).		• Probability carer doesn't administer treatment with Buccolam. • Probability of failed delivery of buccal midazolam.

Data sources

Model structure: The model was analysed from the perspective of 7 European countries (Scotland, Wales, Germany, France, Spain, Italy, Switzerland) with the model originally constructed for the Scottish HTA perspective. The treatment pathway for each country was different, and elicited from clinicians (and parent surveys for Scotland and Wales), in terms of the rescue medication used in each country (and that makes up the 'standard care' comparator of each country);the probabilities associated with administration failure; whether parents can administer other doses; whether patient goes to hospital, and are admitted.

A discrete event simulation that estimated the frequency and location of occurrence of seizures, and a decision tree that assessed the treatment pathway when a child had a seizure. By estimating the frequency and location of prolonged seizures the discrete event simulation enabled the estimate of drug wastage and the probability that rescue medication was not present which then enabled the decision tree to calculate the costs and health consequences following the seizure. The discrete event simulation simulated 5000 patients for each treatment. For each of these patients, the frequency, location of seizures and the initial store of drugs at each location were simulated at the start of the model. The availability of medication at each location was then adjusted by the occurrence of seizures within the model time horizon. If the model reached a point where drugs were disposed of due to expiry, then the value of the disposed products were calculated, and new

products ordered as replacements. The decision tree had the following possible chance nodes: whether medication was available; if treatment was administered by parent/caregiver and if it was successful; if seizure lasted >10 mins if treatment was given; whether care plan recommended giving second dose if seizure lasted > 10 mins; whether child had repeat seizure if seizure lasted >10 mins; if an ambulance was called and whether: ambulance could administer treatment; whether patient was taken to hospital and if they were admitted; if they were admitted then whether they were admitted to intensive care, and other inputs like the assumptions behind wastage. A time horizon of 1 year was used.

Health outcomes: Probability of further seizure and of seizure cessation taken from McIntyre et al 2005[115] which was a UK randomised study comparing buccal midazolam to rectal diazepam. Assumptions made about Buccolam efficacy with buccal midazolam and other forms of administration. Model comparators other than buccal midazolam assumed to be as effective as rectal diazepam. Effectiveness of intervention derived from a Delphi panel of clinicians (e.g., bigger chance of successful administration with buccolam) and can vary by country depending on treatment pathway.

Quality-of-life weights: QALY decrement associated with a seizure based on duration of seizure and recovery time, and utility during that time. Utility values used in the Scottish model were used based on clinicians asked to value health states on behalf of patients using the EQ-5D. but these values were adjusted by the panel of clinicians to reflect their country perspectives. Estimates of proportion cognitively impaired varied by country, and these had different utilities. Duration of seizure taken from McIntyre study and differed by type of drug. Duration of recovery estimated by clinicians and varied by country. **Cost sources:** Cost of buccal Midazolam also includes a £20 sourcing fee per prescription as it is a 'special' because it was unlicensed at the time of the analysis. Drug costs of UK perspectives from BNF and cost of hospital admission and ambulance callouts from NHS reference costs 2011-12. Costs of other perspective from national sources. Includes estimation of drug wastage, because Buccal midazolam is supplied in bottles containing multiple doses, so it cannot be spread across possible locations and much of the product is not used before expiry leading to wastage, whereas Buccolam comes in separate doses. Where the product expired before all of it is used then the remaining cost of the product is calculated, and new product ordered but assumed that where all the product has been used there would be no further wastage at that location for the rest of the model.

Comments

Source of funding: ViroPharma (manufacturers of Buccolam). **Limitations:** Has a UK perspective, and EQ-5D but filled in by clinicians not patients or their parents/carers. Costs out of date: Buccal Midazolam in particular based on current BNF costs this would be more expensive now because only comes in one pre-filled syringe. But costs depend on dose and how it is packaged (separate pre-filled multiple syringes or not) so uncertainty about cost effectiveness based on which buccal product is used as there are generic versions available which are not listed in the BNF. Funded by manufacturers. Most inputs elicited from surveys and are assumptions. **Other:**

Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

H.2 Add on Therapies

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies Monotherapy

Reference	Excluded study reason
Abou-Khalil 2013[2]	Comparison does not match protocol: autoinjector placebo
Ag Sguder 2016[3]	Incorrect study design; retrospective cohort
Agarwal 2007[4]	Incorrect interventions
Amiri-Nikpour 2018[8]	Incorrect interventions
Amouian 2014[9]	Non-English language publication (Arabic)
Appleton 2004[11]	NMA, references checked
Arya 2015[12]	NMA, reference checked
Banta- Banzali 2012[14]	Conference abstract
Bauerschmidt 2017[15]	Incorrect study design; non-systematic review
Bayrlee 2015[16]	Incorrect study design; non-systematic review
Baysun 2005[17]	Incorrect population
Bebin 1994[18]	Conference abstract
Beghi 2018[19]	Incorrect study design; health economic study
Bergin 2008[20]	Incorrect study design; non-systematic review
Bhattacharyya 2006[21]	Study analysed according to seizure number not patient data
Bleck 2013[22]	Incorrect study design; study protocol of unpublished study
Brigo 2012[33]	Systematic review, references checked
Brigo 2013[28]	Systematic review, references checked
Brigo 2015[31]	Incorrect comparisons; intranasal versus buccal of same drug
Brigo 2015[32]	Systematic review, references checked
Brigo 2016[24]	Systematic review, references checked
Brigo 2016[25]	Systematic review, references checked
Brigo 2017[26]	Systematic review, references checked
Brigo 2018[27]	Systematic review of non-randomised studies
Brigo 2019[29]	Systematic review, references checked
Cereghino 1998[35]	Incorrect population
Cereghino 2002[34]	Incorrect population
Chakravarthi 2014[37]	Incorrect interventions-
Chakravarthi 2015[36]	Incorrect interventions -
Chen 2011[42]	Incorrect interventions
Chitsaz 2013[43]	Incorrect interventions
Collins 2003[44]	Incorrect interventions
Dalziel 2017[47]	Incorrect interventions
Dalziel 2019[46]	Incorrect interventions
de 2010[49]	Incorrect study design; longitudinal cross over
de Assis 2012[48]	Incorrect study design; non-systematic review

Reference	Excluded study reason
DeToledo 2000[51]	Incorrect study design; non-systematic review
Doshi 2010[52]	Systematic review, references checked
Dreifuss 1998[53]	Incorrect population
Fa Yyazi 2012[54]	Incorrect population
Fallah 2007[55]	Incorrect interventions
Farrokh 2019[56]	Systematic review, references checked
Fitzgerald 2003[58]	Incorrect study design; retrospective observational study
Gilad 2008[60]	Incorrect population
Glauser 2016[61]	Systematic review, references checked
Gomes 2018[62]	Systematic review includes observational studies data and no quality assurance
Gujjar 2017[63]	Incorrect interventions
Gunawan 2015[64]	Incorrect population
Gunawan 2015[64]	Incorrect population
Hofler 2013[66]	Systematic review of non-randomized studies
Holsti 2010[67]	Incorrect population
Holsti 2010[68]	Incorrect population
Huertas Gonzalez 2019[69]	Non-English language publication (Spanish)
Husain 2015[70]	Unavailable
Isguder 2014[71]	Incorrect study design; retrospective cohort
Jain 2016[72]	Systematic review of population does not match protocol
Javadzadeh 2012[73]	Incorrect population
Jenkinson 2011[74]	Incorrect study design; literature review
Kapur 2019[75]	Incorrect interventions
Kellinghaus 2015[76]	Non-randomised observational registry study of consecutive cases
Kellinghaus 201[77]	Incorrect study design; registry data
Khajeh 2018[78]	Incorrect population
Kinirons 2008[79]	Incorrect study design; literature review
Knake 2008[81]	Incorrect study design; retrospective
Kriel 1991[84]	Incorrect study design; questionnaire results
Kriel 1999[85]	Incorrect interventions
Kriel 2009[83]	Incorrect study design; commentary
Ku 2018[86]	Incorrect study design; diazepam analysis only
Lalji 1967[88]	Incorrect study design; non-randomised study
Lambrechtsen 2008[89]	Incorrect study design; retrospective
Langer 2014[90]	Incorrect study design; retrospective
Lee 2005[93]	Incorrect study population
Lee 2016[94]	Commentary on discontinued study
Legros 2014[95]	Incorrect comparisons; comparing doses
Leppik 1983[96]	Incorrect interventions
Liu 2012[99]	Systematic review, references checked
Lombroso 1989[100]	Incorrect study design; non-randomised studies
Lowenstein 1988[105]	Incorrect study design; retrospective and prospective cohort of patients
Lowenstein 1999[104]	Unavailable abstract

Reference	Excluded study reason
Lowenstein 2001[103]	Incorrect study design; protocol
Lowenstein 2003[102]	Unavailable
Lowenstein 2005[101]	Incorrect study design; literature review
Lyttle 2017[106]	Incorrect interventions-
Lyttle 2019[107]	Incorrect interventions
Mahmoud 2018[108]	Systematic review; incorrect study designs, all non-randomised studies
Mahmoudian 2006[109]	Incorrect study design; case control study
Malamiri 2012[111]	Incorrect interventions
Malamiri 2012[111]	Incorrect interventions
Masapu 2018[113]	Incorrect interventions
Mayer 2002[114]	Incorrect study design; retrospective cohort study
McKee 2015[116]	Incorrect study design; review
McMullan 2010[117]	Systematic review, references checked
McTague 2012[118]	Incorrect study design; observational study
McTague 2018[119]	Systematic review, references checked
Mehta 2007[120]	Incorrect interventions
Menon 2013[121]	Incorrect study design; literature review
Misra 2017[122]	Incorrect interventions
Misra 2016[124]	Incorrect comparisons
Misra 2017[123]	Unavailable
Mittal 2006[127]	Incorrect population
Morales 2015[129]	Incorrect study design; observational study
Muhlhofer 2019[131]	Incorrect study design; observational study
Mundlamuri 2015[132]	Incorrect study population
Murdoch 2007[133]	Systematic review, references checked
Murthy 2006[134]	Incorrect study design; literature review
Navarro 2011[136]	Incorrect study design; protocol
Navarro 2016[137]	Incorrect study design, comparisons
Neligan 2010[138]	Systematic review, references checked
Nene 2019[139]	Incorrect study design, comparison
Newey 2017[140]	Incorrect study design; safety study
Ngampoopun 2018[141]	Incorrect study design; observational study
Niermeijer 2003[143]	Incorrect study design; literature review
Otto 1968[147]	Incorrect study design; abstract only
Owusu 2019[148]	Incorrect study design; retrospective
Pang 2005[149]	Incorrect study design; literature review
Papavasiliou 2004[150]	Incorrect study design; case series
Parviainen 2007[151]	Incorrect study design
Pinto 2016[152]	Population numbers not specified to allow detailed interpretation
Poplawska 2015[153]	Incorrect study design; literature review
Portela 2015[154]	Incorrect population
Prabhakar 2013[155]	Systematic review, references checked
Prasad 2001[156]	Incorrect study design; retrospective

Reference	Excluded study reason
Prasad 2007[157]	Systematic review, references checked
Prasad 2013[159]	Incorrect interventions
Prasad 2014[158]	Systematic review, references checked
Qureshi 2002[160]	Incorrect study design; comparative audit
Rajiv 2019[161]	Systematic review; looked at case studies
Rantsch 2011[162]	Incorrect study design; retrospective cohort study
Rantsch 2013[163]	Incorrect study design; retrospective
Raspall-Chaure 2006[164]	Systematic review, references checked
Reif 2018[165]	Incorrect study design; case report
Remy 1992[166]	Incorrect population
Reznik 2016[167]	Incorrect study design; literature review
Rosenow 2002[168]	Incorrect study design; review
Rossetti 2004[172]	Incorrect study design; retrospective
Rossetti 2008[170]	Incorrect study design; observational study
Rossetti 2011[171]	Incorrect interventions
Rossetti 2018[169]	Incorrect study design; literature review
Ruegg 2003[173]	Incorrect study design; literature review
Sabers 2013[174]	Incorrect interventions
Sanchez Fernandez 2014[175]	Incorrect study design; literature review
Sanchez Fernandez 2019[176]	Incorrect study design; economic analysis
Santamarina 2013[177]	Incorrect study design; retrospective
Scott 1999[178]	Unclear analysis of results
Shah 2005[180]	Incorrect population
Shaner 1985[181]	Incorrect study design; abstract
Shaner 1988[182]	Incorrect study design; non-randomised study
Shibata 2016[183]	Incorrect study design; non-randomised study
Shorvon 2011[185]	Incorrect study design; literature review
Shorvon 2011[186]	Incorrect study design; literature review
Shorvon 2012[184]	Incorrect study design; literature review
Silbergleit 2013[188]	Incorrect study design; literature review
Singh 2009[191]	Incorrect study design; literature review
Singhi 2002[192]	Incorrect interventions
Sirven 2003[193]	Incorrect study design; literature review
Sivakumar 2015[194]	Incorrect study design; retrospective
Skinner 2010[195]	Incorrect study design; case series
Smith 1971[197]	Incorrect study design; case series
Smith 2001[196]	Incorrect study design; literature review
Sofou 2009[198]	Systematic review, references checked
Sorel 1981[199]	Incorrect study design; non-randomised studies
Sreenath 2010[200]	Incorrect study design; observational study
Stecker 1998[201]	Incorrect study design; retrospective and prospective, non-randomised study
Strzelczyk 2015[203]	Incorrect study population

Reference	Excluded study reason
Strzelczyk 2016[202]	Incorrect study population
Strzelczyk 2017[204]	Systematic review, references checked
Su 2016[205]	Incorrect interventions
Sutter 2013[210]	Incorrect study design; observational study
Sutter 2014[209]	Incorrect study design; observational study
Sutter 2015[208]	Incorrect study design; literature review
Sutter 2017[206]	Incorrect study design; observational study
Sutter 2018[207]	Systematic review, references checked
Talukdar 2009[211]	Incorrect population
Tan 2010[212]	Incorrect study objective; looking at causes of status epilepticus
Tanabe 2011[213]	Incorrect study population
Tasker 2014[214]	Incorrect study design; literature review
Thomson 2005[216]	Incorrect study design; literature review
Towne 1999[218]	Incorrect study design; non-randomised study
Treiman 1985[219]	Incorrect study design; abstract only
Treiman 1991[220]	Unavailable abstract
Trinka 2009[222]	Unavailable
Trinka 2009[224]	Systematic review, references checked
Trinka 2011[223]	Incorrect study design; literature review
Trinka 2014[227]	Systematic review, references checked
Trinka 2015[225]	Incorrect study design; literature review
Trinka 2016[226]	Incorrect study design; literature review
Trinka 2017[228]	Incorrect study design; literature review
Tripathi 2010[229]	Incorrect study design; non-randomised study
Uges 2009[230]	Incorrect study design; non-randomised study
Uppal 2018[231]	Incorrect study objectives; assessing protocol adherence
Vasquez 2019[232]	Incorrect study design, literature review
Vohra 2015[234]	Incorrect comparisons; comparing endotracheal intubation
Vossler 2019[235]	Incorrect study design; commentary
Walker 2003[237]	Incorrect study design; literature review
Walker 2005[236]	Incorrect study design; literature review
Wheless 2008[242]	Incorrect study design; literature review
Wheless 2010[240]	Incorrect study design, literature review
Wheless 2019[241]	Incorrect study design; non-randomised study
Wilkes 2013[244]	Incorrect study design; literature review
Wilkes 2014[243]	Systematic review; incorrect study designs
Willems 2019[245]	Systematic review, references individually checked; incorrect study designs
Won 2019[246]	Incorrect study design; non-randomised study
Wongjirattikarn 2019[247]	Incorrect study population
Yasiry 2014[249]	Systematic review, references checked
Zelano 2012[250]	Systematic review, references checked
Zhang 2019[251]	Systematic review; incorrect comparisons
Zhao 2016[252]	NMA, references individually checked

1

I.2 Excluded clinical studies Add on therapies

Reference	Exclusion reason
Abdelgadir 2020[1]	Systematic review: references checked
Abou-Khalil 2013[2]	Comparison does not match protocol: autoinjector placebo
Ag Sguder 2016[3]	Incorrect study design; retrospective cohort
Ahmed 2006[5]	Incorrect intervention
Alamrani 2021[6]	Systematic review: references checked
Alldredge 2001[7]	Incorrect intervention
Amouian 2014[9]	Non-English language publication (Arabic)
Appleton 1995[10]	Incorrect intervention
Appleton 2004[11]	NMA; incorrect population
Arya 2015[12]	NMA; incorrect population
Ashrafi 2010[13]	Incorrect intervention
Banta- Banzali 2012[14]	Conference abstract
Bauerschmidt 2017[15]	Incorrect study design; non-systematic review
Bayrlee 2015[16]	Incorrect study design; non-systematic review
Baysun 2005[17]	Incorrect population
Bebin 1994[18]	Conference abstract
Beghi 2018[19]	Incorrect study design; health economic study
Bergin 2008[20]	Incorrect study design; non-systematic review
Bhattacharyya 2006[21]	Study analysed according to seizure number not patient data
Bleck 2013[22]	Incorrect study design; study protocol of unpublished study
Brigo 2012[33]	Systematic review; incorrect population
Brigo 2013[28]	Systematic review; incorrect population
Brigo 2015[31]	Incorrect population
Brigo 2015[32]	Systematic review; incorrect population
Brigo 2016[24]	Systematic review; incorrect population
Brigo 2016[25]	Systematic review; incorrect population
Brigo 2017[26]	Systematic review; incorrect population
Brigo 2018[27]	Systematic review; incorrect population
Brigo 2018[30]	Systematic review; incorrect population
Brigo 2019[29]	Systematic review; incorrect population
Cereghino 1998[35]	Incorrect population
Cereghino 2002[34]	Incorrect population
Chamberlain 2014[40]	Incorrect intervention
Chamberlain 1997[38]	Incorrect intervention
Chamberlain 2020 [39]	Duplicate study of data from ESETT trial broken into age categories
Collins 2003[44]	Incorrect interventions
de 2010[49]	Incorrect study design; longitudinal cross over
de Assis 2012[48]	Incorrect study design; non-systematic review
DeMott 2020[50]	Systematic review: references checked
DeToledo 2000[51]	Incorrect study design; non-systematic review
Doshi 2010[52]	Systematic review; incorrect population
Dreifuss 1998[53]	Incorrect population
Fa Yyazi 2012[54]	Incorrect population

Reference	Exclusion reason
Farrokh 2019[56]	Systematic review; incorrect population
Fisgin 2018[57]	Incorrect intervention
Fitzgerald 2003[58]	Incorrect study design; retrospective observational study
Gathwala 2012[59]	Incorrect intervention
Gilad 2008[60]	Incorrect population
Glauser 2016[61]	Systematic review; incorrect population
Gomes 2018[62]	Systematic review; incorrect population
Gunawan 2015[64]	Incorrect population
Gunawan 2015[64]	Incorrect population NB Duplicate
Hofler 2013[66]	Systematic review of non-randomized studies
Holsti 2010[67]	Incorrect population
Holsti 2010[68]	Incorrect population
Huertas Gonzalez 2019[69]	Non-English language publication (Spanish)
Husain 2015[70]	Unavailable
Isguder 2014[71]	Incorrect study design; retrospective cohort
Jain 2016[72]	Systematic review; incorrect population
Javadzadeh 2012[73]	Incorrect population
Jenkinson 2011[74]	Incorrect study design; literature review
Kapur 2019[75]	Duplicate paper of ESETT trial
Kellinghaus 2015[76]	Non-randomised observational registry study of consecutive cases
Kellinghaus 2018[77]	Incorrect study design; registry data
Khajeh 2018[78]	Incorrect population
Kinirons 2008[79]	Incorrect study design; literature review
Klowak 2021[80]	Systematic review: references checked
Knake 2008[81]	Incorrect study design; retrospective
Kobata 2020[82]	Systematic review: references checked
Kriel 1991[84]	Incorrect study design; questionnaire results
Kriel 1999[85]	Incorrect interventions
Kriel 2009[83]	Incorrect study design; commentary
Ku 2018[86]	Incorrect study design; diazepam analysis only
Lahat 2000[87]	Incorrect intervention
Lalji 1967[88]	Incorrect study design; non-randomised study
Lambrechtsen 2008[89]	Incorrect study design; retrospective
Langer 2014[90]	Incorrect study design; retrospective
Lee 2005[93]	Incorrect study population
Lee 2016[94]	Commentary on discontinued study
Legros 2014[95]	Incorrect comparisons; comparing doses
Leppik 1983[96]	Incorrect interventions
Li 2020[97]	Systematic review: references checked
Liampas 2021[98]	Systematic review: references checked
Liu 2012[99]	Systematic review; incorrect population
Lombroso 1989[100]	Incorrect study design; non-randomised studies
Lowenstein 1988[105]	Incorrect study design; retrospective and prospective cohort of patients
Lowenstein 1999[104]	Unavailable abstract

Reference	Exclusion reason
Lowenstein 2001[103]	Protocol
Lowenstein 2003[102]	Unavailable
Lowenstein 2005[101]	Incorrect study design; literature review
Mahmoud 2018[108]	Systematic review; incorrect population
Mahmoudian 2006[109]	Incorrect study design; case control study
Malu 2014[112]	Incorrect intervention
Mayer 2002[114]	Incorrect study design; retrospective cohort study
McIntyre 2005[115]	Incorrect intervention
McKee 2015[116]	Incorrect study design; review
McMullan 2010[117]	Systematic review; incorrect population
McTague 2012[118]	Incorrect study design; observational study
McTague 2018[119]	Systematic review; incorrect population
Menon 2013[121]	Incorrect study design; literature review
Misra 2016[124]	Incorrect comparisons
Misra 2017[123]	Unavailable
Misra 2012[125]	Incorrect intervention
Misra 2006[126]	Incorrect intervention
Mittal 2006[127]	Incorrect population
Momen 2015[128]	Incorrect intervention
Morales 2015[129]	Incorrect study design; observational study
Mpimbaza 2008[130]	Incorrect intervention
Muhlhofer 2019[131]	Incorrect study design; observational study
Mundlamuri 2015[132]	Incorrect study population
Murdoch 2007[133]	Systematic review; incorrect population
Murthy 2006[134]	Incorrect study design; literature review
Navarro 2011[136]	Incorrect study design; protocol
Navarro 2016[137]	Incorrect study design, comparisons
Neligan 2010[138]	Systematic review; incorrect population
Nene 2019[139]	Incorrect study design, comparison
Newey 2017[140]	Incorrect study design; safety study
Ngampoopun 2018[141]	Incorrect study design; observational study
Niermeijer 2003[143]	Incorrect study design; literature review
Ochoa 2021[145]	Incorrect study design; literature review
Otto 1968[147]	Incorrect study design; abstract only
Owusu 2019[148]	Incorrect study design; retrospective
Pang 2005[149]	Incorrect study design; literature review
Papavasiliou 2004[150]	Incorrect study design; case series
Parviainen 2007[151]	Incorrect study design
Pinto 2016[152]	Population numbers not specified to allow detailed interpretation
Poplawska 2015[153]	Incorrect study design; literature review
Portela 2015[154]	Incorrect population
Prabhakar 2013[155]	Systematic review; incorrect population
Prasad 2001[156]	Incorrect study design; retrospective
Prasad 2007[157]	Systematic review; incorrect population
Prasad 2013[159]	Incorrect interventions

Reference	Exclusion reason
Prasad 2014[158]	Systematic review; incorrect population
Qureshi 2002[160]	Incorrect study design; comparative audit
Rajiv 2019[161]	Systematic review; incorrect population
Rantsch 2011[162]	Incorrect study design; retrospective cohort study
Rantsch 2013[163]	Incorrect study design; retrospective
Raspall-Chaure 2006[164]	Systematic review; incorrect population
Reif 2018[165]	Incorrect study design; case report
Remy 1992[166]	Incorrect population
Reznik 2016[167]	Incorrect study design; literature review
Rosenow 2002[168]	Incorrect study design; review
Rossetti 2004[172]	Incorrect study design; retrospective
Rossetti 2008[170]	Incorrect study design; observational study
Rossetti 2011[171]	Incorrect interventions
Rossetti 2018[169]	Incorrect study design; literature review
Ruegg 2003[173]	Incorrect study design; literature review
Sabers 2013[174]	Incorrect interventions
Sanchez Fernandez 2014[175]	Incorrect study design; literature review
Sanchez Fernandez 2019[176]	Incorrect study design; economic analysis
Santamarina 2013[177]	Incorrect study design; retrospective
Scott 1999[178]	Unclear analysis of results
Shah 2005 [180]	Incorrect population
Shaner 1985[181]	Incorrect study design; abstract
Shaner 1988[182]	Incorrect study design; non-randomised study
Shibata 2016[183]	Incorrect study design; non-randomised study
Shorvon 2011[185]	Incorrect study design; literature review
Shorvon 2011[186]	Incorrect study design; literature review
Shorvon 2012[184]	Incorrect study design; literature review
Silbergleit 2013[188]	Incorrect study design; literature review
Silbergleit 2012[187]	Incorrect intervention
Silbergleit 2011[189]	Incorrect intervention
Singh 2009[191]	Incorrect study design; literature review
Singh 2018[190]	Incorrect study population
Sirven 2003[193]	Incorrect study design; literature review
Sivakumar 2015[194]	Incorrect study design; retrospective
Skinner 2010[195]	Incorrect study design; case series
Smith 1971[197]	Incorrect study design; case series
Smith 2001[196]	Incorrect study design; literature review
Sofou 2009[198]	Systematic review; incorrect population
Sorel 1981[199]	Incorrect study design; non-randomised studies
Sreenath 2010[200]	Incorrect study design; observational study
Stecker 1998[201]	Incorrect study design; retrospective and prospective, non-randomised study
Strzelczyk 2015[203]	Incorrect study population
Strzelczyk 2016[202]	Incorrect study population
Strzelczyk 2017[204]	Systematic review; incorrect population
Sutter 2013[210]	Incorrect study design; observational study

Reference	Exclusion reason
Sutter 2014[209]	Incorrect study design; observational study
Sutter 2015[208]	Incorrect study design; literature review
Sutter 2017[206]	Incorrect study design; observational study
Sutter 2018[207]	Systematic review; incorrect population
Talukdar 2009 [211]	Incorrect population
Tan 2010[212]	Incorrect study objective; looking at causes of status epilepticus
Tanabe 2011[213]	Incorrect study population
Tasker 2014[214]	Incorrect study design; literature review
Thakker 2013[215]	Incorrect intervention
Thomson 2005[216]	Incorrect study design; literature review
Tonekaboni 2012[217]	Incorrect intervention
Towne 1999[218]	Incorrect study design; non-randomised study
Treiman 1985[219]	Incorrect study design; abstract only
Treiman 1991[220]	Unavailable abstract
Treiman 1998[221]	Incorrect intervention
Trinka 2009[222]	Unavailable
Trinka 2009[224]	Systematic review; incorrect population
Trinka 2011[223]	Incorrect study design; literature review
Trinka 2014[227]	Systematic review; incorrect population
Trinka 2015[225]	Incorrect study design; literature review
Trinka 2016[226]	Incorrect study design; literature review
Trinka 2017[228]	Incorrect study design; literature review
Tripathi 2010 [229]	Incorrect study design; non-randomised study
Uges 2009[230]	Incorrect study design; non-randomised study
Uppal 2018[231]	Incorrect study objectives; assessing protocol adherence
Vasquez 2019[232]	Incorrect study design, literature review
Vohra 2015[234]	Incorrect comparisons; comparing endotracheal intubation
Vossler 2019[235]	Incorrect study design; commentary
Walker 2003[237]	Incorrect study design; literature review
Walker 2005[236]	Incorrect study design; literature review
Welch 2015[239]	Incorrect intervention
Wheless 2008[242]	Incorrect study design; literature review
Wheless 2010[240]	Incorrect study design, literature review
Wheless 2019[241]	Incorrect study design; non-randomised study
Wilkes 2013[244]	Incorrect study design; literature review
Wilkes 2014[243]	Systematic review; incorrect study designs
Willems 2019[245]	Systematic review; incorrect population
Won 2019[246]	Incorrect study design; non-randomised study
Wongjirattikarn 2019[247]	Incorrect study population
Xuu 2020[248]	Systematic review: references checked
Yasiry 2014[249]	Systematic review; incorrect population
Zelano 2012[250]	Systematic review; incorrect population
Zhang 2019[251]	Systematic review; incorrect comparisons
Zhao 2016[252]	NMA; incorrect population

I.3 Excluded health economic studies Monotherapy

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 45: Studies excluded from the health economic review

Reference	Reason for exclusion
Beghi 2018[19]	Excluded as rated not applicable as it updates the inputs of Lee 2014 related to the Italian perspective, but only calculates total costs for the country so is actually a budget impact analysis.

I.4 Excluded health economic studies Add on therapies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 46: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	