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Anti-seizure medications for neonates with seizures (Review)

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Anti-seizure medications for neonates with seizures.
Cochrane Database of Systematic Reviews 2023, Issue 10. Art. No.: CD014967.
DOI: 10.1002/14651858.CD014967.pub2.

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[Intervention Review]

Anti-seizure medications for neonates with seizures

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Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 10, 2023.

Citation: Abiramalatha T, Thanigainathan S, Ramaswamy VV, Pressler R, Brigo F, Hartmann H. Anti-seizure medications for neonates with seizures. *Cochrane Database of Systematic Reviews* 2023, Issue 10. Art. No.: CD014967. DOI: 10.1002/14651858.CD014967.pub2.

ABSTRACT

Background

Newborn infants are more prone to seizures than older children and adults. The neuronal injury caused by seizures in neonates often results in long-term neurodevelopmental sequelae. There are several options for anti-seizure medications (ASMs) in neonates. However, the ideal choice of first-, second- and third-line ASM is still unclear. Further, many other aspects of seizure management such as whether ASMs should be initiated for only-electrographic seizures and how long to continue the ASM once seizure control is achieved are elusive.

Objectives

1. To assess whether any ASM is more or less effective than an alternative ASM (both ASMs used as first-, second- or third-line treatment) in achieving seizure control and improving neurodevelopmental outcomes in neonates with seizures. We analysed EEG-confirmed seizures and clinically-diagnosed seizures separately.

2. To assess maintenance therapy with ASM versus no maintenance therapy after achieving seizure control. We analysed EEG-confirmed seizures and clinically-diagnosed seizures separately.

3. To assess treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates.

Search methods

We searched MEDLINE, Embase, CENTRAL, Epistemonikos and three databases in May 2022 and June 2023. These searches were not limited other than by study design to trials.

Selection criteria

We included randomised controlled trials (RCTs) that included neonates with EEG-confirmed or clinically diagnosed seizures and compared (1) any ASM versus an alternative ASM, (2) maintenance therapy with ASM versus no maintenance therapy, and (3) treatment of clinical or EEG seizures versus treatment of clinical seizures alone.

Data collection and analysis

Two review authors assessed trial eligibility, risk of bias and independently extracted data. We analysed treatment effects in individual trials and reported risk ratio (RR) for dichotomous data, and mean difference (MD) for continuous data, with respective 95% confidence interval (CI). We used GRADE to assess the certainty of evidence.

Main results

We included 18 trials (1342 infants) in this review.

Phenobarbital versus levetiracetam as first-line ASM in EEG-confirmed neonatal seizures (one trial)

Phenobarbital is probably more effective than levetiracetam in achieving seizure control after first loading dose (RR 2.32, 95% CI 1.63 to 3.30; 106 participants; moderate-certainty evidence), and after maximal loading dose (RR 2.83, 95% CI 1.78 to 4.50; 106 participants; moderate-certainty evidence). However, we are uncertain about the effect of phenobarbital when compared to levetiracetam on mortality before discharge (RR 0.30, 95% CI 0.04 to 2.52; 106 participants; very low-certainty evidence), requirement of mechanical ventilation (RR 1.21, 95% CI 0.76 to 1.91; 106 participants; very low-certainty evidence), sedation/drowsiness (RR 1.74, 95% CI 0.68 to 4.44; 106 participants; very low-certainty evidence) and epilepsy post-discharge (RR 0.92, 95% CI 0.48 to 1.76; 106 participants; very low-certainty evidence). The trial did not report on mortality or neurodevelopmental disability at 18 to 24 months.

Phenobarbital versus phenytoin as first-line ASM in EEG-confirmed neonatal seizures (one trial)

We are uncertain about the effect of phenobarbital versus phenytoin on achieving seizure control after maximal loading dose of ASM (RR 0.97, 95% CI 0.54 to 1.72; 59 participants; very low-certainty evidence). The trial did not report on mortality or neurodevelopmental disability at 18 to 24 months.

Maintenance therapy with ASM versus no maintenance therapy in clinically diagnosed neonatal seizures (two trials)

We are uncertain about the effect of short-term maintenance therapy with ASM versus no maintenance therapy during the hospital stay (but discontinued before discharge) on the risk of repeat seizures before hospital discharge (RR 0.76, 95% CI 0.56 to 1.01; 373 participants; very low-certainty evidence). Maintenance therapy with ASM compared to no maintenance therapy may have little or no effect on mortality before discharge (RR 0.69, 95% CI 0.39 to 1.22; 373 participants; low-certainty evidence), mortality at 18 to 24 months (RR 0.94, 95% CI 0.34 to 2.61; 111 participants; low-certainty evidence), neurodevelopmental disability at 18 to 24 months (RR 0.89, 95% CI 0.13 to 6.12; 108 participants; low-certainty evidence) and epilepsy post-discharge (RR 3.18, 95% CI 0.69 to 14.72; 126 participants; low-certainty evidence).

Treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates (two trials)

Treatment of both clinical and electrographic seizures when compared to treating clinical seizures alone may have little or no effect on seizure burden during hospitalisation (MD -1871.16, 95% CI -4525.05 to 782.73; 68 participants; low-certainty evidence), mortality before discharge (RR 0.59, 95% CI 0.28 to 1.27; 68 participants; low-certainty evidence) and epilepsy post-discharge (RR 0.75, 95% CI 0.12 to 4.73; 35 participants; low-certainty evidence). The trials did not report on mortality or neurodevelopmental disability at 18 to 24 months.

We report data from the most important comparisons here; readers are directed to Results and Summary of Findings tables for all comparisons.

Authors' conclusions

Phenobarbital as a first-line ASM is probably more effective than levetiracetam in achieving seizure control after the first loading dose and after the maximal loading dose of ASM (moderate-certainty evidence). Phenobarbital + bumetanide may have little or no difference in achieving seizure control when compared to phenobarbital alone (low-certainty evidence). Limited data and very low-certainty evidence preclude us from drawing any reasonable conclusion on the effect of using one ASM versus another on other short- and long-term outcomes.

In neonates who achieve seizure control after the first loading dose of phenobarbital, maintenance therapy compared to no maintenance ASM may have little or no effect on all-cause mortality before discharge, mortality by 18 to 24 months, neurodevelopmental disability by 18 to 24 months and epilepsy post-discharge (low-certainty evidence).

In neonates with hypoxic-ischaemic encephalopathy, treatment of both clinical and electrographic seizures when compared to treating clinical seizures alone may have little or no effect on seizure burden during hospitalisation, all-cause mortality before discharge and epilepsy post-discharge (low-certainty evidence).

All findings of this review apply only to term and late preterm neonates.

We need well-designed RCTs for each of the three objectives of this review to improve the precision of the results. These RCTs should use EEG to diagnose seizures and should be adequately powered to assess long-term neurodevelopmental outcomes. We need separate RCTs evaluating the choice of ASM in preterm infants.

PLAIN LANGUAGE SUMMARY

Medication to treat fits in newborn babies

Review questions

What medication can be used effectively and safely to treat seizures in newborns?

How long should the medication for seizures be continued once started?

Should we treat seizures that are seen only on the EEG?

Note:

EEG is a test to analyse the electrical activity of the brain. It identifies seizure activity as well.

Phenobarbital and levetiracetam are anti-seizure medications used in newborns.

'Maintenance treatment' refers to continuing the anti-seizure medication at a smaller dose, once seizures are stopped with a larger dose of the medication.

Key messages

Phenobarbital is probably more effective than levetiracetam in achieving seizure control in newborns. However, we are uncertain about the effect of phenobarbital compared to levetiracetam on other outcomes.

Maintenance treatment with anti-seizure medication during hospital stay and treating seizures only identified on EEG may or may not result in better outcomes in newborns.

Background

Newborns are more prone to develop seizures when compared to older children and adults. The brain damage caused by seizures in newborns is associated with cerebral palsy, intellectual disability, learning problems and a tendency to develop epilepsy in the future. There are only a few options for medications to treat seizures in newborns, and we do not know which is the ideal medication to use first, second or third. Similarly, whether to treat the seizures that are seen only on EEG and how long to continue the anti-seizure medication is also not clear.

What did we want to find?

We looked for evidence from studies that assessed one medication versus another to treat seizures in newborns, studies that evaluated whether maintenance doses of anti-seizure medication should be continued or not, and studies that assessed whether to treat seizures that were identified only on EEG.

What did we do?

We searched for studies that evaluated the effects of medications on treating seizures in newborns. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We identified 18 trials (including 1342 newborns).

Phenobarbital is probably more effective than levetiracetam in achieving seizure control in newborns. However, we are uncertain about the effect of phenobarbital on other outcomes such as death before discharge, requirement for invasive ventilation, sleepiness and epilepsy after discharge.

Maintenance therapy with anti-seizure medication during hospital stay compared to no maintenance therapy may or may not result in better outcomes for newborns. Similarly, treating seizures only identified on EEG may or may not result in better outcomes.

What are the limitations of the evidence?

We are moderately confident that phenobarbital is better than levetiracetam in achieving seizure control. The confidence for the estimates of all other comparisons and outcomes is low to very low. More studies are needed to synthesise strong evidence on medications to treat seizures in newborns.

How up-to-date is this evidence?

Evidence is up-to-date as of June 2023.

Summary of findings 1. Summary of findings table - Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures

Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures

Patient or population: neonates with EEG-confirmed seizures
Setting: Neonatal intensive care unit
Intervention: phenobarbital as first-line ASM
Comparison: levetiracetam as first-line ASM

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with levetiracetam as first-line ASM	Risk with phenobarbital as first-line ASM				
Proportion of infants who achieve seizure control after the first loading dose of ASM	359 per 1000	**834 per 1000** (586 to 1000)	**RR 2.32** (1.63 to 3.30)	106 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	
Proportion of infants who achieve seizure control after the maximal loading dose of ASM	283 per 1000	**801 per 1000** (504 to 1000)	**RR 2.83** (1.78 to 4.50)	83 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	
Mortality or neurodevelopment disability at 18 to 24 months' corrected age - not reported	-	-	-	-	-	The trial did not report this outcome.
Mortality before hospital discharge	78 per 1000	**23 per 1000** (3 to 197)	**RR 0.30** (0.04 to 2.52)	106 (1 RCT)	⊕⊖⊖⊖ Very low[b,c]	
Requirement of mechanical ventilation	375 per 1000	**454 per 1000** (285 to 716)	**RR 1.21** (0.76 to 1.91)	106 (1 RCT)	⊕⊖⊖⊖ Very low[b,c]	
Proportion of infants who develop sedation or drowsiness	109 per 1000	**190 per 1000** (74 to 486)	**RR 1.74** (0.68 to 4.44)	106 (1 RCT)	⊕⊖⊖⊖ Very low[b,c]	
Proportion of infants who develop epilepsy post-discharge	481 per 1000	**443 per 1000** (231 to 847)	**RR 0.92** (0.48 to 1.76)	45 (1 RCT)	⊕⊖⊖⊖ Very low[b,c]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_438900176882570386.

[a] Downgraded by one level for serious imprecision due to small small size not meeting the 'Optimal Information Size' criteria
[b] Downgraded by one level for indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well.
[c] Downgraded by two levels for very serious imprecision due to very low sample size and event rate not meeting the 'Optimal Information Size' criteria

Summary of findings 2. Summary of findings table - Phenobarbital versus levetiracetam as first-line ASM for clinically diagnosed neonatal seizures

Phenobarbital versus levetiracetam as first-line ASM for clinically diagnosed neonatal seizures

Patient or population: clinically diagnosed neonatal seizures
Setting: Neonatal intensive care unit
Intervention: phenobarbital as first-line ASM
Comparison: levetiracetam as first-line ASM

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with levetiracetam as first-line ASM	Risk with phenobarbital as first-line ASM				
Proportion of infants who achieve seizure control after first loading dose of ASM	443 per 1000	**306 per 1000** (244 to 381)	**RR 0.69** (0.55 to 0.86)	286 (3 RCTs)	⊕⊖⊖⊖ Very low[a,b]	
Proportion of infants who achieve seizure control after maximal loading dose of ASM	777 per 1000	**451 per 1000** (365 to 559)	**RR 0.58** (0.47 to 0.72)	260 (3 RCTs)	⊕⊖⊖⊖ Very low[b,c]	
Mortality or neurodevelopment disability at 18 to 24 months' corrected age - not reported	-	-	-	-	-	This outcome was not reported in any included trial
Mortality before hospital discharge	82 per 1000	**116 per 1000** (67 to 200)	**RR 1.41** (0.82 to 2.43)	452 (6 RCTs)	⊕⊕⊖⊖ Low[d,e]	

Requirement of mechanical ventilation	5 per 1000	**11 per 1000** (3 to 49)	**RR 2.20** (0.50 to 9.68)	394 (5 RCTs)	⊕⊖⊖⊖ Very low[d,f]
Proportion of infants who develop sedation or drowsiness	54 per 1000	**102 per 1000** (36 to 292)	**RR 1.88** (0.66 to 5.37)	180 (2 RCTs)	⊕⊖⊖⊖ Very low[c,d,e,g]
Proportion of infants who develop epilepsy post discharge	133 per 1000	**67 per 1000** (7 to 659)	**RR 0.50** (0.05 to 4.94)	30 (1 RCT)	⊕⊖⊖⊖ Very low[f,h]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_442643727142716799.

[a] Downgraded by two levels for very serious risk of bias due to 'high risk of bias' in 2 trials and some concerns in the other trial
[b] Downgraded by one level for serious imprecision due to small sample size not meeting the 'Optimal Information Size' criterion
[c] Downgraded by two levels for very serious risk of bias due to high risk of bias in all included studies
[d] Downgraded by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well
[e] Downgraded by one level for serious imprecision due to low event rate not meeting the 'Optimal Information Size' criteria
[f] Downgraded by two levels for very serious imprecision due to single digit event rate
[g] Downgraded by one level for serious inconsistency due to substantial heterogeneity
[h] Downgraded by two levels for very serious risk of bias due to high risk of bias in the only included study

Summary of findings 3. Summary of findings table - Phenobarbital versus phenytoin as first-line ASM for EEG-confirmed neonatal seizures

Phenobarbital versus phenytoin as first-line ASM for EEG-confirmed neonatal seizures

Patient or population: neonates with EEG-confirmed seizures
Setting: Neonatal intensive care unit
Intervention: phenobarbital as first-line ASM
Comparison: phenytoin as first-line ASM

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with phenytoin as first-line ASM	Risk with phenobarbital as first-line ASM				
Proportion of infants who achieve seizure control after the first loading dose of ASM - not reported	-	-	-	-	-	The trial did not report this outcome
Proportion of infants who achieve seizure control after the maximal loading dose of ASM	448 per 1000	**435 per 1000** (242 to 771)	**RR 0.97** (0.54 to 1.72)	59 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	
Mortality or neurodevelopmental disability at 18 to 24 months' corrected age - not reported	-	-	-	-	-	The trial did not report this outcome

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_438951560046041157.

[a] Downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial
[b] Downgraded by two levels for very serious imprecision due to very low sample size and event rate not meeting the 'Optimal Information Size' criteria

Summary of findings 4. Summary of findings table - Phenobarbital versus phenytoin as first-line ASM for clinically diagnosed neonatal seizures

Phenobarbital versus phenytoin as first-line ASM for clinically diagnosed neonatal seizures

Patient or population: neonates with clinically diagnosed seizures
Setting: Neonatal intensive care unit
Intervention: phenobarbital as first-line ASM

Comparison: phenytoin as first-line ASM

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with phenytoin as first-line ASM	Risk with phenobarbital as first-line ASM				
Proportion of infants who achieve seizure control after first loading dose of ASM	356 per 1000	**683 per 1000** (498 to 939)	**RR 1.92** (1.40 to 2.64)	179 (2 RCTs)	⊕⊕⊖⊖ Low[a,b]	
Proportion of infants who achieve seizure control after maximal loading dose - not reported	-	-	-	-	-	Neither of the two included trials reported this outcome.
Mortality or neurodevelopmental disability at 18 to 24 months' corrected age - not reported	-	-	-	-	-	Neither of the two included trials reported this outcome.
Mortality before hospital discharge	211 per 1000	**281 per 1000** (167 to 477)	**RR 1.33** (0.79 to 2.26)	179 (2 RCTs)	⊕⊖⊖⊖ Very low[c,d,e]	
Requirement of mechanical ventilation	0 per 1000	**0 per 1000** (0 to 0)	**RR 7.13** (0.38 to 134.78)	109 (1 RCT)	⊕⊖⊖⊖ Very low[d,f]	
Proportion of infants who develop sedation or drowsiness	0 per 1000	**0 per 1000** (0 to 0)	**RR 23.00** (1.41 to 375.77)	70 (1 RCT)	⊕⊖⊖⊖ Very low[d,f,g]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_438949398863786458.

[a] Downgraded by one level for serious risk of bias as the trial contributing > 50% weighting to the estimate has a high risk of overall bias
[b] Downgraded by one level for serious inconsistency as there was considerable heterogeneity (I2 = 96%)
[c] Downgraded by one level for serious inconsistency as there was substantial heterogeneity (I2=82%)
[d] Downgraded by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well
[e] Downgraded by one level for serious imprecision for sample size and event rate not meeting the 'Optimal Information Size' criteria
[f] Downgraded by two levels for very serious imprecision due to very low sample size and event rate not meeting the 'Optimal Information Size' criteria
[g] Downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial

Summary of findings 5. Summary of findings table - Phenobarbital versus Lorazepam as first-line ASM for clinically diagnosed neonatal seizures

Phenobarbital versus Lorazepam as first-line ASM for clinically diagnosed neonatal seizures

Patient or population: Neonates with clinically diagnosed seizures
Setting: Neonatal intensive care unit
Intervention: Phenobarbital as first-line ASM
Comparison: Lorazepam as first-line ASM

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Lorazepam as first-line ASM	Risk with Phenobarbital as first-line ASM				
Proportion of infants who achieve seizure control after the first loading dose of ASM	889 per 1000	**631 per 1000** (471 to 836)	**RR 0.71** (0.53 to 0.94)	71 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	
Proportion of infants who achieve seizure control after the maximal loading dose of ASM - not reported	-	-	-	-	-	The included trial did not report this outcome
Mortality or neurodevelopmental disability at 18 to 24 months' corrected age - not reported	-	-	-	-	-	The included trial did not report this outcome.
Mortality before hospital discharge	194 per 1000	**342 per 1000** (154 to 768)	**RR 1.76** (0.79 to 3.95)	71 (1 RCT)	⊕⊖⊖⊖ Very low[a,c,d]	
Proportion of infants who develop sedation or drowsiness	56 per 1000	**314 per 1000** (75 to 1000)	**RR 5.66** (1.35 to 23.71)	71 (1 RCT)	⊕⊖⊖⊖ Very low[a,c,d]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_438956545731624502.

[a] Downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial
[b] Downgraded by one level for serious imprecision for sample size and event rate not meeting the 'Optimal Information Size' criteria
[c] Downgraded by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well
[d] Downgraded by two levels for very serious imprecision due to very low sample size and event rate not meeting the 'Optimal Information Size' criteria

Summary of findings 6. Summary of findings table - Phenytoin versus lorazepam as first-line ASM for clinically diagnosed neonatal seizures

Phenytoin versus lorazepam as first-line ASM for clinically diagnosed neonatal seizures

Patient or population: neonates with clinically diagnosed seizures
Setting: Neonatal intensive care unit
Intervention: phenytoin as first-line ASM
Comparison: lorazepam as first-line ASM

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lorazepam as first-line ASM	Risk with phenytoin as first-line ASM				
Proportion of infants who achieve seizure control after the first loading dose of ASM	889 per 1000	**684 per 1000** (533 to 880)	**RR 0.77** (0.60 to 0.99)	71 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	
Proportion of infants who achieve seizure control after the maximal loading dose of ASM - not reported	-	-	-	-	-	The included trial did not report this outcome.

Mortality or neurodevelopmental disability at 18 to 24 months' corrected age - not reported	-	-	-	-	-	The included trial did not report this outcome.
Mortality before hospital discharge	194 per 1000	**86 per 1000** (23 to 305)	**RR 0.44** (0.12 to 1.57)	71 (1 RCT)	⊕⊖⊖⊖ Very low[a,c,d]	
Proportion of infants who develop sedation or drowsiness	56 per 1000	**12 per 1000** (1 to 229)	**RR 0.21** (0.01 to 4.13)	71 (1 RCT)	⊕⊖⊖⊖ Very low[a,c,d]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_438956906630512363.

[a] Downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial
[b] Downgraded by one level for serious imprecision for sample size and event rate not meeting the 'Optimal Information Size' criteria
[c] Downgraded by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well.
[d] Downgraded by two levels for very serious imprecision due to very low sample size and event rate not meeting the 'Optimal Information Size' criteria

Summary of findings 7. Summary of findings table - Phenobarbital + bumetanide versus phenobarbital alone for EEG-confirmed neonatal seizures

Phenobarbital + bumetanide versus phenobarbital alone for EEG-confirmed neonatal seizures

Patient or population: neonates with EEG-confirmed seizures
Setting: Neonatal intensive care unit
Intervention: phenobarbital + bumetanide
Comparison: phenobarbital alone

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with phenobarbital alone	Risk with phenobarbital + bumetanide				
Proportion of infants who achieve seizure control after the first loading dose of ASM	313 per 1000	**297 per 1000** (116 to 750)	**RR 0.95** (0.37 to 2.40)	43 (1 RCT)	⊕⊕⊖⊖ Low[a]	
Proportion of infants who achieve seizure control after the maximal loading dose of the ASM - not reported	-	-	-	-	-	The included trial did not report this outcome.
Mortality or neurodevelopmental disability at 18 to 24 months' corrected age - not reported	-	-	-	-	-	The included trial did not report this outcome.
Mortality before hospital discharge	188 per 1000	**38 per 1000** (4 to 326)	**RR 0.20** (0.02 to 1.74)	43 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	
Cognitive impairment at 18-24 months	300 per 1000	**159 per 1000** (39 to 645)	**RR 0.53** (0.13 to 2.15)	29 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	
Requirement of mechanical ventilation	Not pooled	Not pooled	Not pooled	(1 RCT)	-	
Proportion of infants who develop epilepsy post-discharge	308 per 1000	**348 per 1000** (132 to 914)	**RR 1.13** (0.43 to 2.97)	39 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_438957230819281917.

[a] Downgraded by two levels for very serious imprecision due to very low sample size and event rate not meeting the 'Optimal Information Size' criteria

[b] Downgraded by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well

Summary of findings 8. Summary of findings table - Lignocaine versus benzodiazepines as second-line ASM for EEG-confirmed neonatal seizures

Lignocaine versus benzodiazepines as second-line ASM for EEG-confirmed neonatal seizures

Patient or population: neonates with EEG-confirmed seizures
Setting: Neonatal intensive care unit
Intervention: lignocaine as second-line ASM
Comparison: benzodiazepines as second-line ASM

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with benzodiazepines as second-line ASM	Risk with lignocaine as second-line ASM				
Proportion of infants who achieve seizure control after first loading dose of ASM - not reported	-	-	-	-	-	The included trial did not report this outcome.
Proportion of infants who achieve seizure control after maximal loading dose of ASM	0 per 1000	**0 per 1000** (0 to 0)	**RR 8.17** (0.52 to 128.42)	11 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	
Mortality or neurodevelopmental disability at 12 months	1000 per 1000	**1000 per 1000** (710 to 1000)	**RR 1.00** (0.71 to 1.41)	10 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c]	
Mortality before hospital discharge	333 per 1000	**400 per 1000** (83 to 1000)	**RR 1.20** (0.25 to 5.71)	11 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c]	
Neurodevelopmental disability at 12 months	600 per 1000	**600 per 1000** (216 to 1000)	**RR 1.00** (0.36 to 2.75)	10 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_438957465149804345.

[a] Downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial
[b] Downgraded by two levels for very serious imprecision due to very low sample size and event rate not meeting the 'Optimal Information Size' criteria
[c] Downgraded by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well

Summary of findings 9. Summary of findings table - Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures

Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures

Patient or population: neonates with clinically diagnosed seizures
Setting: Neonatal intensive care unit
Intervention: maintenance ASM after achieving seizure control
Comparison: no maintenance ASM after achieving seizure control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no maintenance ASM after achieving seizure control	Risk with maintenance ASM after achieving seizure control				
Proportion of infants with repeat seizure before hospital discharge	353 per 1000	**268 per 1000** (198 to 356)	**RR 0.76** (0.56 to 1.01)	373 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b]	
Mortality or neurodevelopmental disability at 18 to 24 months' corrected age - not reported	-	-	-	-	-	Neither of the two included studies reported this outcome.
Mortality before hospital discharge	139 per 1000	**96 per 1000** (54 to 170)	**RR 0.69** (0.39 to 1.22)	373 (2 RCTs)	⊕⊕⊖⊖ Low[b]	
Mortality at 18-24 months	121 per 1000	**113 per 1000** (41 to 315)	**RR 0.94** (0.34 to 2.61)	111 (1 RCT)	⊕⊕⊖⊖ Low[b]	

Neurodevelopmental disability at 18-24 months	39 per 1000	**35 per 1000** (5 to 240)	**RR 0.89** (0.13 to 6.12)	108 (1 RCT)	⊕⊕⊖⊖ Low[b]
Proportion of infants who develop epilepsy post-discharge	33 per 1000	**106 per 1000** (23 to 491)	**RR 3.18** (0.69 to 14.72)	126 (1 RCT)	⊕⊕⊖⊖ Low[b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_438158727822576253.

[a] Downgraded by one level for risk of bias due to 'some concerns' in the risk of bias in both the included studies
[b] Downgraded by two levels for very serious imprecision due to very low sample size and event rate not meeting the 'Optimal Information Size' criteria

Summary of findings 10. Summary of findings table - Treatment of clinical and electrographic seizures versus treatment of clinical seizures alone in neonates

Treatment of clinical and electrographic seizures versus treatment of clinical seizures alone in neonates

Patient or population: neonates
Setting: Neonatal intensive care unit
Intervention: treatment of clinical and electrographic seizures
Comparison: treatment of clinical seizures alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with treatment of clinical seizures alone	Risk with treatment of clinical and electrographic seizures				
Seizure burden during hospitalisation	The mean seizure burden during hospitalisation was **0**	MD **1871.16 lower** (4525.05 lower to 782.73 higher)	-	68 (2 RCTs)	⊕⊕⊖⊖ Low[a]	

Mortality or neurodevelopmental disability at 18 to 24 months' corrected age - not reported	-	-	-	-	-	The included trial did not report this outcome.
Mortality before hospital discharge	345 per 1000	**203 per 1000** (97 to 438)	**RR 0.59** (0.28 to 1.27)	68 (2 RCTs)	⊕⊕⊖⊖ Low[a]	
Proportion of infants who develop epilepsy post-discharge	133 per 1000	**100 per 1000** (16 to 631)	**RR 0.75** (0.12 to 4.73)	35 (1 RCT)	⊕⊕⊖⊖ Low[a]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
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See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_438901735468111265.

[a] Downgraded by two levels for very serious imprecision due to very low sample size and event rate not meeting the 'Optimal Information Size' criteria

BACKGROUND

Description of the condition

The term 'seizure' is defined as a transient occurrence of signs or symptoms, due to abnormal excessive or synchronous neuronal activity in the brain (Fisher 2005). However, this definition does not include electrographic-only seizures. The American Clinical Neurophysiology Society (ACNS) defines electrographic seizures in neonates based on electroencephalogram (EEG) as "a sudden, abnormal EEG event, defined by a repetitive and evolving pattern with a minimum 2 μV peak-to-peak voltage and duration of at least 10 seconds" (Pressler 2021; Tsuchida 2013). The incidence of neonatal seizures ranges from 1.5 to 5.5 per 1000 live births in term infants and 11 to 19 per 1000 live births in preterm infants (Buraniqi 2017; Lanska 1995; Ronen 1999; Saliba 1999; Vasudevan 2013). The clinical manifestations of neonatal seizures are motor (clonic, tonic, myoclonic, spasms or automatisms), non-motor (autonomic or behavioural arrest) or a combination of both (sequential) (Pressler 2021).

Hypoxic-ischaemic encephalopathy (HIE), a form of neonatal encephalopathy caused by perinatal asphyxia, is the most common cause of neonatal seizures. The other major causes are focal ischaemic lesions (stroke), intracranial haemorrhage, central nervous system (CNS) infections, CNS malformations, inborn errors of metabolism and genetic causes (Lanska 1995; Ronen 1999; Tekgul 2006). Though most neonatal seizures are acutely provoked (i.e. they are caused by an acute brain insult), 10% to 20% are the first manifestation of epilepsy (Shellhaas 2017).

A newborn infant's brain is more vulnerable to developing seizures compared to the brain of older children and adults. This is due to the imbalance between excitatory and inhibitory neurotransmitters; there is excessive excitatory glutamate activity and deficient inhibitory gamma-aminobutyric acid (GABA) activity in the immature neonatal brain. Moreover, GABA exerts a paradoxical excitatory action in the neonatal brain due to delayed expression of potassium chloride co-transporter 2 (KCC2) receptors, which result in high intracellular chloride concentration and depolarisation (Dzhala 2003; Dzhala 2005; Huttenlocher 1982; Khazipov 2004; Takashima 1980).

Neonatal seizures are diagnosed either clinically, or by recording the electrical activity of the brain using an EEG. Recent evidence suggests that clinical diagnosis of seizures is not reliable (Malone 2009; Pellegrin 2019; Soul 2019). It is now believed that all, or nearly all, seizures have an EEG correlate, while half of all seizures have no clinical correlate (Nash 2011). Continuous, video-assisted recording of conventional electroencephalography (cEEG) is considered the gold standard for diagnosing and monitoring neonatal seizures (Clancy 1996; McCoy 2013; Wusthoff 2013). Amplitude-integrated EEG (aEEG) is an alternative, though it may not detect all seizures due to the limited number of scalp electrodes and modification of signals (Glass 2013). Automated seizure detection using machine learning technology is increasingly used in neonatal intensive care units (NICUs) to improve the seizure detection rate (Pavel 2020). However, though EEG confirmation of seizures is considered essential, treatment of seizures based on clinical diagnosis does exist as a practice in many centres, especially in resource-limited settings.

Seizures substantially increase the metabolic demand of the CNS (Younkin 1986). This results in a marked decline in brain high-energy phosphates and glucose, causing neuronal injury by energy deprivation (Fujikawa 1988). In addition, the cardiorespiratory compromise and fluctuating arterial pressure during a seizure result in hypoxic and ischaemic injury to the brain, causing neuronal cell death (Clozel 1985; McDonald 1990). The neuronal injury caused by seizures often results in long-term neurological sequelae such as cerebral palsy, cognitive impairment, learning disabilities and future epilepsy (Pisani 2012; Ronen 2007; Yildiz 2012).

Description of the intervention

Once the immediately correctable causes of neonatal seizures, such as hypoglycaemia and hypocalcaemia, are addressed, there are several options for anti-seizure medications (ASMs). Phenobarbitone, phenytoin and levetiracetam are the commonly used ASMs in neonates (Slaughter 2013; Van Rooij 2013). Drugs such as lidocaine and midazolam are used as infusions for seizures that are refractory (difficult to control) (Abend 2011; Fürwentsches 2010; Slaughter 2013; Van Rooij 2013). Newer drugs, such as topiramate and bumetanide, have also been explored for the treatment of neonatal seizures (Glass 2011; Jensen 2009; Pressler 2015).

Anti-seizure medications act through various mechanisms, the main ones being blockage of voltage-gated ion channels, GABA-mediated neuronal inhibition, and blockage of glutamatergic excitatory pathways. Barbiturates and benzodiazepines enhance GABA-mediated inhibition by modulating the permeability of chloride channels. Vigabatrin potentiates GABA inhibition by blocking GABA transaminase, the GABA-degrading enzyme. Gabapentin acts by enhancing GABA-mediated inhibition and possibly also by inactivating sodium channels. It has been suggested that drugs that act through GABA may be less effective in neonatal seizures because of the paradoxical chloride response in GABA receptors, and the overall reduced GABA receptor expression in neonates (Dulac 2013; Jensen 2009). However, this has never been confirmed in humans.

Phenytoin, carbamazepine and lamotrigine cause blockage of voltage-gated sodium channels and inhibit repetitive neuronal firing. Levetiracetam and brivaracetam act by binding to the synaptic vesicle protein, (SV2A) in the brain, resulting in modulation of synaptic neurotransmitter release (Abou-Khalil 2008). Valproate acts by multiple mechanisms, such as blocking voltage-gated sodium channels, interfering with glutamate-mediated excitation, and increasing GABA concentration in the brain by influencing GABA synthesis and breakdown. Remacemide acts by blocking N-methyl-D-aspartate (NMDA) receptors and voltage-gated sodium channels. Topiramate acts on multiple sites, including GABA receptors, glutamate receptors, L-type calcium receptors, and possibly voltage-gated sodium channels (Brodie 1996; Gidal 1999; Meldrum 1996; Taylor 1995).

How the intervention might work

The aim of treating neonatal seizures with an ASM is to reduce seizure burden and stop progression to status epilepticus with the main aim of stopping seizures. This is assumed to reduce the risk of long-term neurodevelopmental impairment (Wirrell 2005; Yager 2002). However, animal experiments indicate that they may cause neuronal apoptosis, and alter neurogenesis

and neural cell migration in the developing brain (Bittigau 2002; Ikonomidou 2010). Further, many ASMs cause significant adverse effects. Phenobarbitone and benzodiazepines can cause respiratory depression and hypoventilation requiring ventilatory support; phenytoin can cause arrhythmias leading to circulatory disturbance; lidocaine can lead to hypotension requiring volume or inotropic support; valproate can cause hepatotoxicity; and other adverse effects of ASMs include nephrotoxicity and free-radical injury (El-Dib 2017; Yozawitz 2017).

Neonatal seizures are difficult to treat with conventional ASMs. This is due to the inadequate development of inhibitory systems and excessive activity of excitatory systems in the developing brain as discussed above, and the lack of novel targets on which these medications can act upon. Studies have shown that neonatal seizures were refractory to first-line drugs in nearly 50% of cases and that an additional 30% failed to respond even when second-line drugs were added (Boylan 2002; Boylan 2004). Studies on phenobarbitone and phenytoin have given conflicting evidence about the efficacy of one medication over the other (Painter 1999; Pathak 2013). Further, the risk of uncoupling (the persistence of electrographic seizures after the suppression of clinical seizures) is well documented with both phenobarbitone and phenytoin (Scher 1993; Scher 2003). This would increase the burden of unrecognised seizures in centres where continuous cEEG monitoring is not used.

Recently, drugs such as levetiracetam, topiramate and bumetanide are being investigated in research trials, with variable benefits. Though these drugs may have the advantage of not causing neuronal apoptosis, data regarding their efficacy, safety and optimal dosing are lacking (Cha 2002; Cleary 2013; Dzhala 2008; Kahle 2009; Kilicdag 2013; Kim 2007; Liu 2004; Liu 2012; Manthey 2005; McHugh 2018; Rao 2018; Sharpe 2020; Talos 2013).

Why it is important to do this review

There is no definitive evidence or guideline on the choice of first-, second- and third-line ASMs in neonates. Furthermore, it is not clear whether ASMs should be initiated for only electrographic seizures, only clinical seizures, or both electrographic and clinical seizures (Booth 2004; Boylan 2013; Slaughter 2013; Srinivasakumar 2015; Van Rooij 2010). Finally, it is unclear how long to continue the ASM for once it is initiated, that is, whether to continue maintenance doses once seizure control is achieved after the loading dose (Saxena 2016).

Given the benefits, as well as the potential harm of using ASMs for neonatal seizures, we have undertaken a Cochrane Review that identifies and appraises data from randomised controlled trials, to provide a synthesis of evidence regarding the efficacy and adverse effects of using ASMs in neonatal seizures and their influence on short-, intermediate- and long-term outcomes.

OBJECTIVES

1. To assess whether any anti-seizure medication (ASM) is more or less effective than an alternative ASM (both ASMs used as first-, second- or third-line treatment) in achieving seizure control and improving neurodevelopmental outcomes in neonates with seizures. We analysed EEG-confirmed seizures and clinically-diagnosed seizures separately.
2. To assess maintenance therapy with ASM versus no maintenance therapy after achieving seizure control. We analysed EEG-confirmed seizures and clinically-diagnosed seizures separately.
3. To assess treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), both parallel-design and cross-over trials*, in this review. We did not identify any quasi- or cluster-RCTs for inclusion in this review.

We included studies on any class of ASMs that are known to be used in neonatal seizures.

We excluded studies on the use of vitamins, medical gas or other interventions such as therapeutic hypothermia, which may have a role in seizure control in neonates. We also excluded trials with prophylactic use of ASMs to prevent neonatal seizures or to improve neurodevelopmental outcomes.

(*See Differences between protocol and review.)

Types of participants

We included newborn infants of any gestational age, gender or ethnicity who were diagnosed with seizures. We included seizures due to any aetiology and treated with any ASM. We included seizures that were:

1. clinical with EEG confirmation (EEG-confirmed clinical seizures or electro-clinical seizures);
2. clinically diagnosed without EEG confirmation (clinically-diagnosed seizures);
3. only electrographic without any clinical manifestation (electrographic-only seizures).

Types of interventions

We compared:

1. any ASM versus an alternative ASM in EEG-confirmed neonatal seizures and clinically-diagnosed neonatal seizures (both ASMs used as first-, second- or third-line treatment);
2. maintenance therapy with ASM versus no maintenance therapy in EEG-confirmed neonatal seizures and clinically-diagnosed neonatal seizures;
3. treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone.

We excluded ASMs used for indications other than neonatal seizures, such as neonatal hyperbilirubinaemia, sedation, or anaesthesia. We analysed EEG-confirmed seizures and clinically-diagnosed seizures separately. This was because appropriate diagnosis of seizures is an essential prerequisite to test the efficacy of ASMs (accurate outcome measure). Therefore, trials that included only EEG-confirmed seizures will provide more reliable data on the outcomes of treatment with ASMs. However, treatment of seizures based on clinical diagnosis is a common practice and could not be excluded, although it is recognised that clinical diagnosis is associated with a high risk of over and under-diagnosis.

Hence, we analysed both EEG-confirmed seizures and clinically-diagnosed seizures in separate comparisons.

Types of outcome measures

Primary outcomes

1. Proportion of infants who achieve seizure control after first or maximal loading dose of the given ASM;
2. Mortality or neurodevelopmental disability at 18 to 24 months' corrected age. Neurodevelopmental disability was defined as one or more of the following: cerebral palsy on clinical examination; developmental delay more than two standard deviations (SDs) below population mean on a standardised test of development; blindness (visual acuity less than 6/60); deafness (any hearing impairment requiring amplification).

(**The outcomes are reported in different ways in the trials. We have mentioned the changes in the reported outcomes, if any, in the*Differences between protocol and review).

Secondary outcomes

1. Mortality before hospital discharge or at any time later;
2. Neurodevelopmental disability at 18 to 24 months' corrected age, defined as one or more of the following: cerebral palsy on clinical examination; developmental delay more than two SDs below population mean on a standardised test of development; blindness (visual acuity less than 6/60); deafness (any hearing impairment requiring amplification);
3. Proportion of infants who develop cognitive impairment at two years or more (defined as a cognitive score below 70 measured using a validated assessment tool);
4. Seizure burden (seizure hours per infant, or minutes per hour of monitoring) during hospitalisation;
5. Proportion of infants with one or more of the following adverse effects related to ASM(s) during hospitalisation:
   a. Requirement for mechanical ventilation;
   b. Sedation or drowsiness;
   c. Arrhythmias causing circulatory disturbance;
   d. Bradycardia;
   e. Hypotension requiring volume or inotropic support;
   f. Shock requiring volume or inotropic support;
   g. Hepatotoxicity resulting in discontinuation of therapy;
   h. Acute kidney injury (of any stage);
   i. Any further individual adverse effects;
6. Proportion of infants with abnormal background pattern in EEG (as defined by the authors) during the ASM treatment and after stopping the ASM;
7. Duration of hospital stay (days);
8. Proportion of infants with persistent seizures or requiring ASM(s) at discharge (or both);
9. Proportion of infants discharged on gavage feeds;
10. Proportion of infants with abnormal neurological examination at discharge: as defined by trialists based on validated tools, or as hypotonia or muscle weakness;
11. Proportion of infants who develop epilepsy post-discharge;
12. Time to establish full oral feeds (days);
13. Proportion of infants who required ≥ 3 ASMs.

Search methods for identification of studies

The Cochrane Neonatal Information Specialist, Chris Cooper, wrote and ran search strategies.

Electronic searches

We searched the following databases in May 2022 with an update search in June 2023. We searched without restrictions on language, publication year, publication type, or publication status.

- Cochrane Central Register of Controlled Trials (CENTRAL), Issue 6, 2023;
- Ovid MEDLINE, MEDALL (1946 to 06 June 2023);
- Ovid Embase (1980 to 2023 Week 22);
- Epistemonikos (registry of systematic reviews) https://www.epistemonikos.org, 7 June 2023.

Search strategies are available in Appendix 1; Appendix 2.

Searching other resources

We identified trial registration records using CENTRAL and by independent searches of the following:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov), 7 June 2023;
- ICTRP--World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int/Default.aspx), 7 June 2023.

We screened the reference lists of included or related, or both, studies (e.g. in the subject area of our review but not eligible for inclusion), and related systematic reviews (e.g. reviews including the population or intervention examined in our review) for studies not identified by the database searches.

Data collection and analysis

Selection of studies

Search results were managed in Endnote. Duplicates were removed using both Endnote and Covidence. Titles and abstracts were assessed in two ways: using Cochrane's Screen4Me (S4M) system (https://community.cochrane.org/sites/default/files/uploads/S4M_Users_FAQs.pdf) and by author screening.

The S4M system includes three levels of assessment for identifying non-RCT records. Of these three levels, we used two: Known Assessments and RCT Classifier (Marshall 2018; Noel-Storr 2020; Thomas 2021). Records remaining after S4M classification were screened independently by two of four authors (TA, ST, VVR and HH). These same authors independently screened the full texts of studies remaining after title/abstract assessment. At any point during the screening process, disagreements were resolved by discussion or by another reviewer. Where a review author was involved in an included study, any decisions regarding inclusion were made by other authors.

We collated multiple reports of the same study so that the study, rather than the reference, was the unit of interest in the review. Information about studies is provided in the following tables: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification); and Characteristics of ongoing studies.

We reported the study selection process in sufficient detail to generate a PRISMA flow diagram (Liberati 2009; Moher 2009).

Data extraction and management

Two review authors (TA and ST) independently extracted, assessed, and coded all data for each study, using a form designed specifically for this review. We collected information regarding the method of randomisation, masking, intervention, stratification, and whether the trial was single- or multi-centre for each included study. We noted information regarding trial participants, including gestational age, type of seizures, aetiology of seizures, and treatment details. We analysed the clinical outcomes noted above in the Types of outcome measures.

We described ongoing studies identified by our search (when available), detailing the primary author, research question(s), methods, and outcome measures, together with an estimate of the reporting date. We reported such studies in the Characteristics of ongoing studies table.

We resolved any disagreements by discussion with a third review author (HH). Should any queries arise or, in cases for which additional data were required, we contacted study investigators/authors for clarification. We replaced any standard error of the mean by the corresponding standard deviation. One review author (TA) entered final data for each study into Review Manager web (RevMan Web 2023), which the other review author (ST) checked. All review authors reviewed the analysis, results and drafted the manuscript.

Assessment of risk of bias in included studies

The review authors (VVR and RP) independently assessed the risk of bias in all included trials using version 2 of the Cochrane Risk of bias tool (RoB 2) (Higgins 2019). We resolved any disagreements by discussion or by consulting a third author (TA).

We assessed the risk of bias for each study outcome using the following Cochrane RoB 2 criteria:

1. bias arising from the randomisation process;
2. bias due to deviations from intended interventions;
3. bias due to missing outcome data;
4. bias in measurement of the outcome;
5. bias in selection of the reported result.

For each domain, a series of signalling questions with answers (yes, probably yes, no information, probably no, or no) determined the risk of bias (low risk, some concerns, or high risk). We included relevant text alongside the judgements to provide supporting information for our decisions. We decided the overall risk of bias for an outcome by its performance in all the domains: the overall judgement was 'some concerns' if we assigned a judgement of 'some concerns' for one domain, and 'high risk' if we assigned a judgement of 'some concerns' for multiple domains or 'high risk' for one (or more) domains.

Measures of treatment effect

We performed the statistical analyses using Review Manager web (RevMan Web 2023). We summarised the data in a meta-analysis if they were sufficiently homogeneous, both clinically and statistically. For dichotomous data, we presented results using risk ratios (RRs) with 95% confidence intervals (CIs). For continuous data, we used the mean difference (MD) when outcomes were measured in the same way between trials.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials. We did not identify any cluster-randomised trial for inclusion in our review.

Dealing with missing data

We requested additional data from the trialists if data on important outcomes were missing or were reported unclearly. We obtained additional data from the authors of five trials (Falsaperla 2019; Jindal 2021; Khan 2020; Sharpe 2020; Soul 2021).

Assessment of heterogeneity

We estimated the treatment effects of individual trials and examined heterogeneity amongst trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. We interpreted the degree of heterogeneity as follows:

1. 0% to 40% might not be important;
2. 30% to 60% may represent moderate heterogeneity;
3. 50% to 90% may represent substantial heterogeneity; and
4. 75% to 100%, indicating considerable heterogeneity.

We explored the possible causes (e.g. differences in study quality, participants, intervention regimens, or outcome assessments) if we identified substantial heterogeneity (i.e. an I^2 value greater than 50%).

Assessment of reporting biases

We assessed reporting bias by comparing the studies' stated primary outcomes and secondary outcomes with the reported outcomes. Where study protocols were available, we compared these to the full publications to determine the likelihood of reporting bias.

As we included fewer than 10 trials in all the meta-analyses, we did not examine a funnel plot for possible publication bias.

Data synthesis

If we identified multiple studies that we considered to be sufficiently similar, we performed meta-analysis using Review Manager web (RevMan Web 2023). We used a fixed-effect model to combine data where it was reasonable to assume that studies were estimating the same underlying treatment effect. If we deemed meta-analysis to be inappropriate, we analysed and interpreted individual trials separately.

Subgroup analysis and investigation of heterogeneity

We explored substantial statistical heterogeneity in the outcomes by visually inspecting the forest plots (Higgins 2020). Where statistical heterogeneity was significant, we interpreted the results of the meta-analyses accordingly; and we downgraded the certainty of evidence in the summary of findings tables, according to the GRADE recommendations (see Summary of findings and assessment of the certainty of the evidence).

Where data were available, we planned to conduct subgroup analyses based on:

1. gestational age (term infants (born at 37 weeks' gestation or greater) versus preterm infants (born at less than 37 weeks' gestation));
2. aetiology of seizure (acquired or discrete CNS injury such as hypoxic-ischaemic encephalopathy, intracranial haemorrhage, stroke or infections versus congenital disorders with ongoing epileptic potential such as metabolic disorders, brain malformations, channelopathies, or other genetic causes).

We did not perform any subgroup analysis as all the included trials were performed on term and late preterm infants, and data based on aetiology of seizures were not available.

Sensitivity analysis

Where we identified substantial heterogeneity, we planned to conduct sensitivity analysis to determine if the findings were affected by inclusion of only those trials considered to have used adequate methodology, i.e. those with a low risk of bias. We planned to report results of sensitivity analyses for primary outcomes only.

However, we did not perform any sensitivity analysis, as it was not required.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence for the following outcomes for all comparisons:

1. proportion of infants who achieve seizure control;
2. mortality or neurodevelopmental disability at 18 to 24 months;
3. mortality (at any time);
4. neurodevelopmental disability at 18 to 24 months;
5. proportion of infants who develop cognitive impairment at three years or more;
6. proportion of infants who develop adverse effects of ASM;
7. proportion of infants who develop epilepsy post-discharge.

(**The outcomes are reported in different ways in the trials. We have mentioned the changes in the reported outcomes, if any, in the*Differences between protocol and review.)

Two review authors (TA and FB) independently assessed the certainty of the evidence for each of the outcomes above. We resolved any disagreements by discussion with a third author (VVR). We considered evidence from RCTs as being high-certainty, and downgraded the assessment by one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used GRADEpro GDT to create 10 summary of findings tables to report the certainty of the evidence for the following comparisons:

1. Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures (Summary of findings 1);
2. Phenobarbital versus levetiracetam as first-line ASM for clinically diagnosed neonatal seizures (Summary of findings 2);
3. Phenobarbital versus phenytoin as first-line ASM for EEG-confirmed neonatal seizures (Summary of findings 3);
4. Phenobarbital versus phenytoin as first-line ASM for clinically diagnosed neonatal seizures (Summary of findings 4);
5. Phenobarbital versus lorazepam as first-line ASM for clinically diagnosed neonatal seizures (Summary of findings 5);
6. Phenytoin versus lorazepam as first-line ASM for clinically diagnosed neonatal seizures (Summary of findings 6);
7. Phenobarbital+bumetanide versus phenobarbital alone as first-line ASM for EEG-confirmed neonatal seizures (Summary of findings 7);
8. Lignocaine versus benzodiazepines as second-line ASM for EEG-confirmed neonatal seizures (Summary of findings 8);
9. Maintenance therapy with ASM versus no maintenance therapy after achieving seizure control for clinically diagnosed neonatal seizures (Summary of findings 9);
10. Treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates (Summary of findings 10).

The GRADE approach results in an assessment of the certainty of a body of evidence in one of the following four grades.

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

RESULTS

Description of studies

Results of the search

The study selection process is available in Figure 1. Searches identified 13,009 references. Of these, we processed 10,950 using Cochrane's Screen4Me (Figure 2; Figure 3). Screen4Me rejected 4475 references as non-RCTs; of the remaining 8534 references, we removed 3166 duplicates, and screened 5368 references. We excluded 5300 based on title/abstract, and reviewed 68 full texts or trial registry records. We included 18 studies (Characteristics of included studies); excluded 30 (Characteristics of excluded studies); classified two as awaiting assessment (Characteristics of studies awaiting classification); and identified 23 ongoing studies (Characteristics of ongoing studies).

Figure 1. Flow diagram

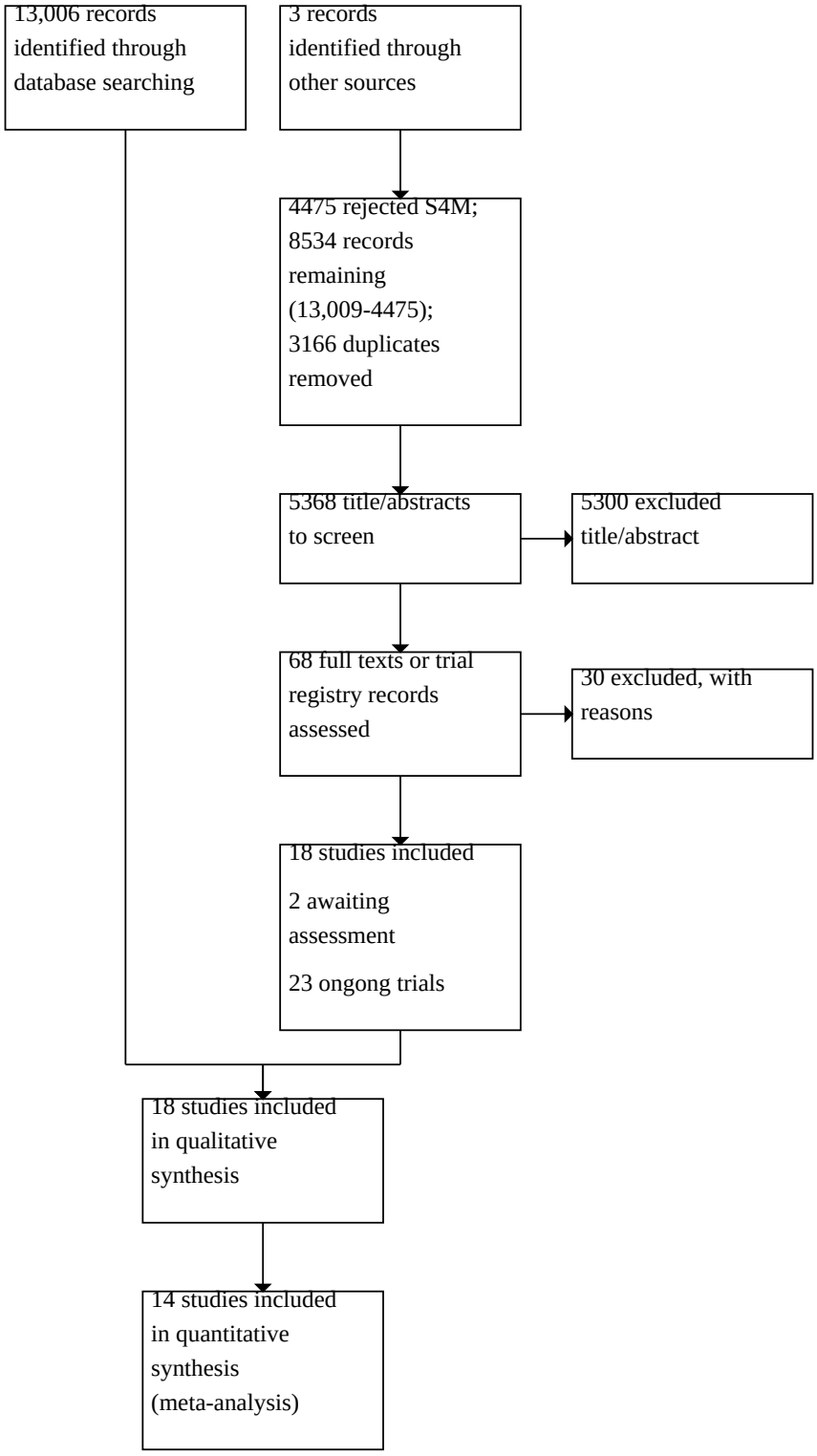


Figure 2. Screen4Me 2022

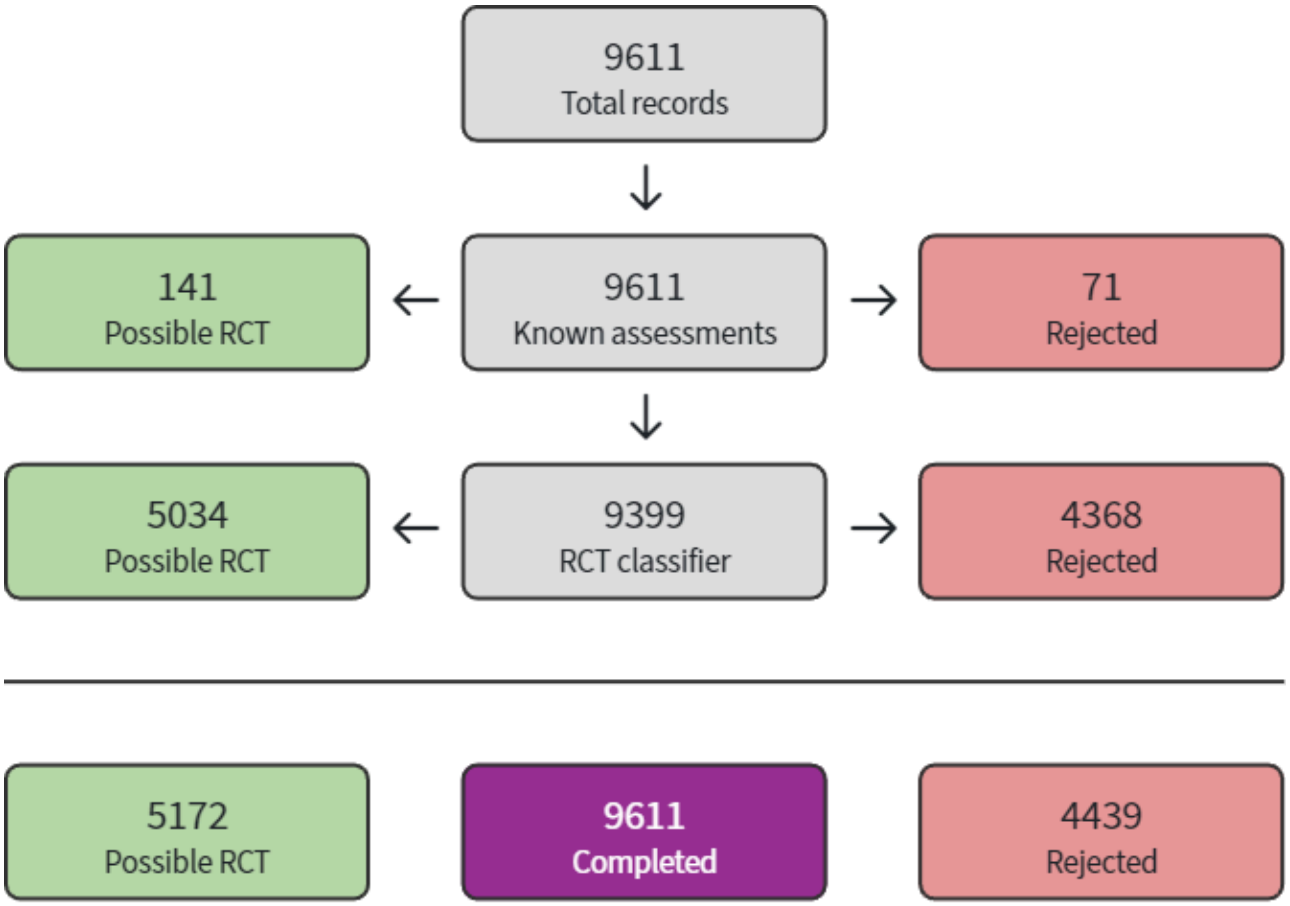
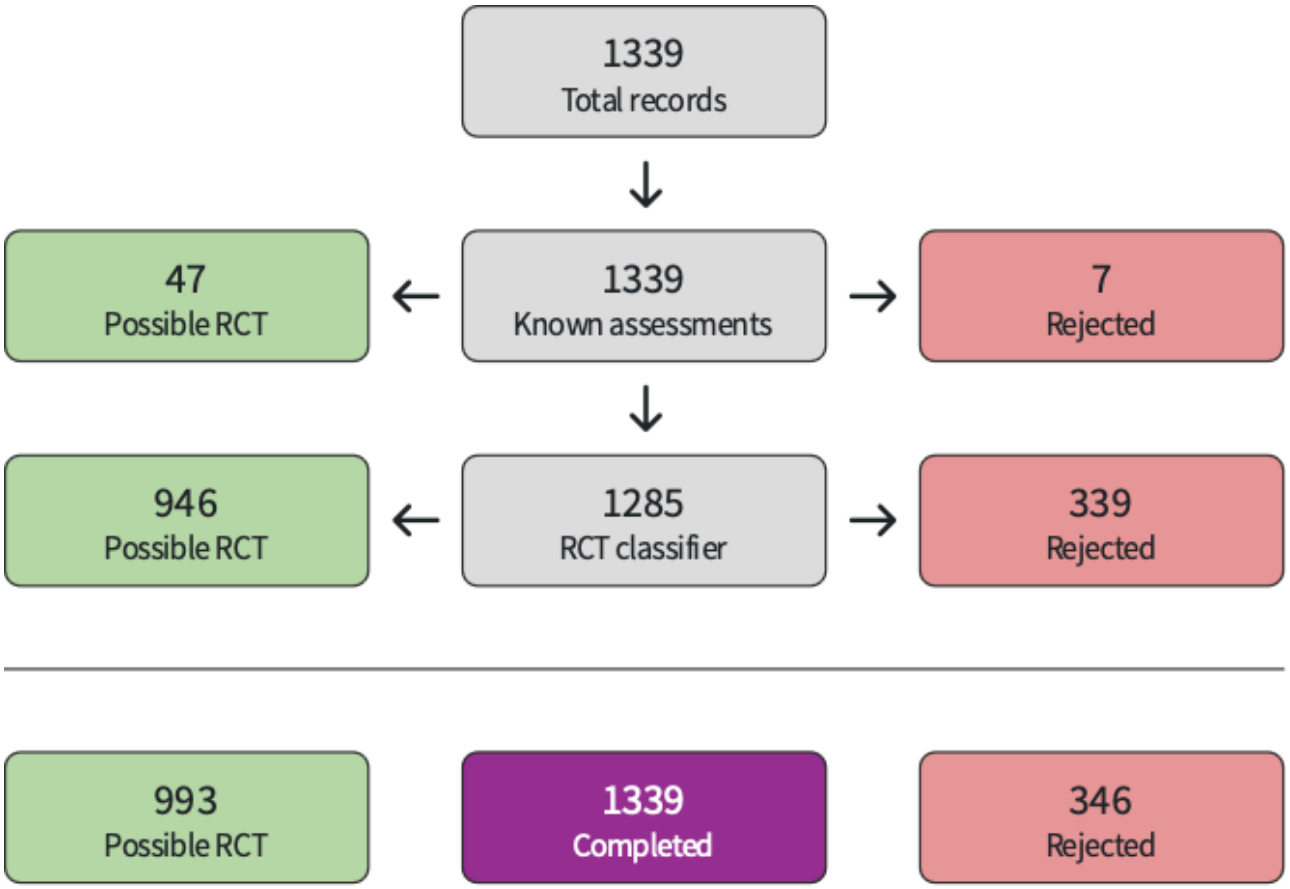


Figure 3. Screen4Me 2023



Comparison of one ASM versus another

We included 18 trials (1342 infants) in our analysis. See Characteristics of included studies.

Phenobarbital versus levetiracetam as first-line ASM

Nine studies (Akeel 2022; Falsaperla 2019; Ghaffar 2020; Gowda 2019; Khan 2020; Perveen 2016; Prakash 2019; Sharpe 2020; Susnerwala 2022), compared phenobarbital versus levetiracetam as first-line ASM. All nine studies had included term and late preterm neonates. While Sharpe 2020 utilised EEG to confirm seizures, the other eight studies used clinical diagnosis of seizures (Akeel 2022; Falsaperla 2019; Ghaffar 2020; Gowda 2019; Khan 2020; Perveen 2016; Prakash 2019; Susnerwala 2022). The aetiology of seizures included all causes except hypoglycaemia and hypocalcaemia in six studies (Akeel 2022; Ghaffar 2020; Gowda 2019; Khan 2020; Prakash 2019; Sharpe 2020); while Perveen 2016 included seizures due to any aetiology. The aetiologies were HIE, intracranial haemorrhage and meningitis in Falsaperla 2019. Susnerwala 2022 included seizures due to HIE alone. Seizure control was defined variably as seizure-free for 24 hours in Akeel 2022; Ghaffar 2020; Gowda 2019, Sharpe 2020 and Susnerwala 2022; 48 hours in Khan 2020; five days in Prakash 2019 and one week in Falsaperla 2019. All nine studies have continued maintenance doses of ASM after achieving seizure control.

While Falsaperla 2019 excluded infants who required an additional ASM for seizure control, the other studies have included infants requiring further ASMs. In Ghaffar 2020; Khan 2020; Perveen 2016 and Sharpe 2020, second and third-line ASMs were chosen as per the NICU protocol or at the discretion of the treating neonatologist. Akeel 2022; Gowda 2019; Prakash 2019 and Susnerwala 2022 are add-on trials (strictly speaking, not cross-over trials as phenobarbital has a long half-life and there was no washout phase), where phenobarbital was used as the second-line drug in the levetiracetam group and vice versa. For the outcomes on efficacy, i.e. 'seizure control after single dose ASM' and 'seizure control after maximum dose ASM', we considered only the monotherapy effect, that is, seizure control after the first-line drug that was randomised. However, for all the other outcomes during further hospital stay, after discharge and for long-term outcomes at 18 to 24 months, we analysed as per the randomisation, and we did not exclude infants who had received other drugs as second- or third- line ASMs. Further, we did not analyse cross-over trials separately, because no study included washout periods due to ethical considerations (See Differences between protocol and review). Further, since we have only three or four drugs that can be used for neonatal seizures, we were of the view that all trials were essentially like cross-over trials, as the authors would have used the comparator drug as a second- or third-line ASM in the intervention group, and vice versa.

The dose of phenobarbital and levetiracetam also varied across the studies. While Falsaperla 2019; Perveen 2016 and Susnerwala

2022 used 20 mg/kg of phenobarbital, Akeel 2022 and Gowda 2019 used 30 mg/kg (20 mg/kg followed by 10 mg/kg); and Ghaffar 2020; Khan 2020; Prakash 2019 and Sharpe 2020 used 40 mg/kg (20 mg/kg followed by 2 doses of 10 mg/kg each). The maintenance dose used was 5 mg/kg/day in all studies. In the levetiracetam group, Falsaperla 2019 and Susnerwala 2022 used only a single loading dose of 20 mg/kg; Khan 2020 and Perveen 2016 used a single loading dose of 50 mg/kg and 60 mg/kg respectively; Prakash 2019 used an initial loading dose of 10 mg/kg and maximal loading dose of 15 mg/kg; Akeel 2022 used an initial loading dose of 20 mg/kg and maximal loading dose of 30 mg//kg; Ghaffar 2020 used an initial loading dose of 30 mg/kg and maximal loading dose of 40 mg/kg, Gowda 2019 used an initial loading dose of 20 mg/kg and maximal loading dose of 40 mg/kg, and Sharpe 2020 used an initial loading dose of 40 mg/kg and maximal loading dose of 60 mg/kg.

Phenobarbital versus phenytoin as first-line ASM

Three studies (Painter 1999; Pathak 2013; Solanki 2015), compared phenobarbital versus phenytoin as first-line ASM. All three studies included term and late preterm neonates. While Painter 1999 utilised EEG to confirm seizures, the two other studies (Pathak 2013; Solanki 2015), used clinical diagnosis of seizures. The aetiology of seizures included all causes except hypoglycaemia and hypocalcaemia in two studies (Pathak 2013; Solanki 2015), while Painter 1999 included seizures due to all causes. Seizure control was defined as stopping of seizures within 2.5 minutes of the loading dose in two studies (Painter 1999; Solanki 2015), while it was defined as seizure control soon after the loading dose in Pathak 2013. One study (Painter 1999), gave maintenance doses after the loading dose, while the other two studies (Pathak 2013; Solanki 2015), did not give maintenance doses of ASM.

Two studies (Painter 1999; Pathak 2013), were cross-over trials where phenytoin was used as the second-line ASM in the phenobarbital group and vice versa. In Solanki 2015, the choice of further ASMs was at the clinician's discretion. Both phenobarbital and phenytoin were used at a dose of 20 mg/kg for loading in Pathak 2013 and Solanki 2015, while Painter 1999 used the dose of ASM required to achieve a serum concentration of 2.5 mcg/mL.

Phenobarbital and phenytoin versus lorazepam as first-line ASM

One study (Solanki 2015), compared phenobarbital and phenytoin versus lorazepam as first-line ASM. The study included term and late preterm neonates, and used only clinical diagnosis of seizures. The aetiology of seizures included all causes except hypoglycaemia and hypocalcaemia. Seizure control was defined as stopping seizures within 2.5 minutes of the loading dose. The choice of further ASMs was at the clinician's discretion. Phenobarbital and phenytoin were used at a dose of 20 mg/kg, while lorazepam was used at a dose of 0.05 mg/kg for loading in the study. The study authors did not administer maintenance doses after the loading dose.

Phenobarbital + bumetanide versus phenobarbital alone as first-line ASM

One study (Soul 2021), compared phenobarbital + bumetanide versus phenobarbital alone. The study included neonates born at ≥ 33 weeks' gestation who had EEG-confirmed seizures. The aetiology of seizures included all causes except hypoglycaemia, hypocalcaemia, and inborn errors of metabolism. Neonates who had seizures despite 20 to < 40 mg/kg of phenobarbital were randomised to phenobarbital alone (5 to 10 mg/kg) or phenobarbital (5 to 10 mg/kg) and bumetanide (0.1 to 0.3 mg/kg). The choice of further ASMs was as per the unit protocol. The study primarily aimed to evaluate the pharmacokinetics and pharmacodynamics of bumetanide. Seizure control was a post hoc outcome.

Lidocaine versus benzodiazepines as second-line ASM

One study (Boylan 2004), compared lidocaine versus benzodiazepines (midazolam or clonazepam) as second-line ASM. The study included both term and preterm neonates who had EEG-confirmed seizures. The aetiology of seizures included HIE, intracranial haemorrhage and meningitis. First-line ASM was phenobarbital, given at 40 mg/kg maximal loading dose. Seizure control was defined as reduction in seizure burden by 80% in 12 hours. Lidocaine was given at a dose of 4 mg/kg over 20 minutes, followed by 2 mg/kg/h, and increased to 4 mg/kg/h if seizure control was not achieved. Midazolam was administered at a dose of 60 µg/kg loading followed by 150 µg/kg/h, and increased up to 300 µg/kg/h after 12 hours if seizure control was not achieved.

Maintenance therapy with ASM versus no maintenance therapy after achieving seizure control

Two trials and 373 infants (Jindal 2021; Saxena 2016), were included in the comparison of short-term maintenance therapy with ASM versus no maintenance therapy for neonatal seizures during hospital stay. Both trials included neonates born at ≥ 34 weeks' gestation and had only clinically-diagnosed seizures. The aetiologies of seizures were perinatal asphyxia, meningitis and intracranial haemorrhage in both trials, while Saxena 2016 also included seizures due to metabolic causes. Both trials included only those neonates who achieved seizure control after a single loading dose of 20 mg/kg of phenobarbital. Infants who required further doses of phenobarbital or other ASMs to achieve seizure control were excluded. The time of randomisation was 12 hours seizure-free after 20 mg//kg phenobarbital in both trials. The duration of maintenance therapy with phenobarbital was five days in one trial (Saxena 2016), while it was until hospital discharge in the other trial (Jindal 2021).

Treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates

Two trials and 68 infants (Srinivasakumar 2015; Van Rooji 2010), were included in the comparison of any ASM treatment versus no treatment for only-electrographic seizures. Both trials were performed on neonates born at ≥ 35 weeks' gestation and both included only neonates with HIE. The ASMs used were phenobarbital, phenytoin and midazolam in Srinivasakumar 2015, while Van Rooji 2010 used phenobarbital, midazolam, lignocaine and clonazepam. The time of randomisation was before the onset of electrographic seizures in Srinivasakumar 2015, though the outcomes were reported only for those neonates who had electrographic seizures. The time of randomisation was after the onset of electrographic seizures in the Van Rooji 2010 study. While Srinivasakumar 2015 used continuous video EEG to diagnose seizures, Van Rooji 2010 used aEEG.

Excluded studies

We excluded 30 studies for the reasons described below. See Characteristics of excluded studies.

Studies without a comparator

Several studies described the effect of a single ASM without a comparator and therefore had to be excluded. Retrospective case series examined the effect of levetiracetam as first-line ASM (Abend 2011; Han 2018; Kanmaz 2021), sodium valproate (Gal 1988), or lidocaine (Favié 2020; Weeke 2016). Uncontrolled cohort studies examined the effect of levetiracetam as first-line medication (Sedighi 2016; Ramantani 2011), or lidocaine (Hellström-Westas 1988). One study describing clinical, neuroimaging, and electrographic predictors of phenobarbital failure in newborns with hypoxic ischaemic encephalopathy and seizures also had to be excluded (Dwivedi 2019). Another study examined the effect of phenobarbital on EEG (Low 2016), without a comparator.

Comparison of one ASM versus another

Phenobarbital versus levetiracetam as first-line ASM

The efficacy of phenobarbital versus levetiracetam was retrospectively compared by six studies, all of which had to be excluded because of the retrospective design (Liu 2020; Maitre 2013; Rao 2018; Thibault 2020; Verwoerd 2022; Wagner 2021). The authors of one study specifically addressed neurodevelopmental outcomes (Maitre 2013); another study focused on newborns undergoing cardiac surgery (Thibault 2020). One cross-sectional study examined neurodevelopment of newborns with seizures following treatment with phenobarbital versus levetiracetam and also had to be excluded because of lack of randomisation (Arican 2020).

Phenobarbital versus other medications as first-line ASM

One RCT comparing the effects of phenobarbital, phenytoin, clonazepam, and sodium valproate was excluded because data were only published as a conference abstract (Rochefort 1989).

Second and third-line ASM

One uncontrolled cohort study compared the effects of phenytoin in newborns with clinical seizures not controlled by phenobarbital as second-line ASM (Jawadekar 1992). This study also addressed the pharmacokinetics of phenobarbital in newborns. Another cohort study examined the effect of midazolam as third-line ASM, without a comparator (Castro Conde 2005). Retrospective studies addressed possible effects of lidocaine or midazolam on newborns with seizures not controlled by phenobarbital (Shany 2007). Pharmacokinetics and effects of bumetanide in newborns with EEG-confirmed seizures not responding to a loading dose of phenobarbital was examined in one study (Pressler 2015). A retrospective study examined the effect of lorazepam as third-line ASM (Deshmukh 1986). The efficacy and safety of midazolam versus levetiracetam as third-line ASM was investigated in one non-randomised study, with no confirmation of seizures by EEG (Jayswal 2021). An uncontrolled cohort study examined the efficacy of oral levetiracetam as third-line ASM in neonates with clinical seizures not responding to phenobarbital and phenytoin (Mollamohammadi 2018).

Maintenance therapy with ASM versus no maintenance therapy after achieving seizure control

Safety of early discontinuation of ASM after acute symptomatic neonatal seizures was retrospectively assessed in one study (Glass 2021). The study found no difference in neurodevelopment or epilepsy at age 24 months amongst children whose ASM was discontinued versus maintained at hospital discharge after resolution of acute symptomatic neonatal seizures. The study was excluded because of its retrospective nature.

Treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates

A RCT examining neurodevelopment following treatment of electrographic-only seizures versus clinical seizures (Hunt 2021) was excluded because seizure detection was based on aEEG alone and assessment of seizure burden was only initiated over 24 hours after birth. Thus, the study design impedes reaching conclusive results regarding the question examined.

Studies awaiting classification

There are two studies awaiting classification (Gyandeep 2023; Mohammadi 2023). They are awaiting classification for the following reason: we need additional data from the study authors to classify the studies and include in the appropriate meta-analyses.

For further details, see Characteristics of studies awaiting classification.

Ongoing studies

There are 23 ongoing studies (ACTRN12622000470796; CTRI/2013/01/003310; CTRI/2013/04/003585; CTRI/2014/06/004659; CTRI/2015/06/005849; CTRI/2016/10/007412; CTRI/2018/04/013161; CTRI/2020/03/023961; CTRI/2021/02/031290; CTRI/2022/09/045658; CTRI/2023/02/049794; IRCT2014070318334N1; IRCT20160523028008N23; IRCT20190526043717N1; IRCT20200115046137N1; IRCT20200131046317N3; IRCT20200528047589N1; IRCT20220619055221N1; NCT01089504; NCT02550028; NCT03107507; NCT04320940; NCT05291455).

For further details, see Characteristics of ongoing studies.

Risk of bias in included studies

Amongst the 18 trials included in the review, the **randomisation process** domain had a low risk of bias for 12 trials (Akeel 2022; Gowda 2019; Jindal 2021; Pathak 2013; Perveen 2016; Prakash 2019; Saxena 2016; Sharpe 2020; Soul 2021; Srinivasakumar 2015; Susnerwala 2022; Van Rooji 2010). The domain had some concerns for four trials (Boylan 2004; Falsaperla 2019; Khan 2020; Ghaffar 2020), as there was no information on allocation concealment, but baseline characteristics did not show any difference between the two groups. The domain had high risk for two trials (Painter 1999; Solanki 2015), as there was no information on allocation concealment and baseline characteristics suggested a mismatch between the two groups despite randomisation.

The domain '**deviation from intended interventions**' had a low risk of bias for all 18 trials, as one was a triple-masked trial (Soul 2021) and, in the other 14 trials, although the personnel were aware of the intervention allocation, there seemed to be no deviations that arose outside the trial context. Also, all the patients were analysed as randomised in these trials.

The domain '**missing outcome data**' also had a low risk of bias for all the trials, as the outcome data were reasonably complete for all randomised patients in 15 trials (Akeel 2022; Boylan 2004; Falsaperla 2019; Ghaffar 2020; Gowda 2019; Jindal 2021; Khan 2020; Painter 1999; Pathak 2013; Perveen 2016; Prakash 2019; Solanki 2015; Soul 2021; Srinivasakumar 2015; Susnerwala 2022). In Sharpe 2020, although there were missing data, analysis methods that corrected for bias, such as sensitivity analyses showing that results were little changed under a range of plausible assumptions about the relationship between the missing value in the outcome and its true value, were performed. In Van Rooji 2010, although nine out of 42 patients randomised were excluded, the reasons for the same were stated, and they did not differ substantially between the groups, thus indicating that the results might not be biassed. In Saxena 2016, data were reasonably complete for all the included patients until hospital discharge. Though many of the enrolled participants were lost to follow-up, it was balanced between the two groups. Hence, it seemed that the result was not biassed as reasons for the loss to follow-up did not differ significantly between the groups.

For the domain '**measurement of outcome**', objective outcomes were scored 'low risk' for all 18 trials. However, for subjective outcomes, only Soul 2021 had a low risk of bias as it was a triple-masked trial. Other trials were scored 'some concerns' for subjective outcomes, as the assessors were aware of the intervention and there was a likelihood of assessment being influenced by the knowledge of the allocation group. For outcomes related to seizure assessment such as seizure control after a single loading dose of ASM, seizure control after maximal loading dose of ASM, and recurrence of seizures before hospital discharge, trials that used EEG/aEEG to diagnose seizures were scored low risk (Boylan 2004; Painter 1999; Sharpe 2020; Srinivasakumar 2015; Van Rooji 2010). Amongst the trials that used clinical diagnosis of seizures, seven trials (Falsaperla 2019; Ghaffar 2020; Gowda 2019; Jindal 2021; Khan 2020; Perveen 2016; Saxena 2016), were scored high risk, as there was no clear definition for different seizure types, how it was differentiated from non-epileptic events and how it was assessed and by whom. Five trials (Akeel 2022; Pathak 2013; Prakash 2019; Solanki 2015; Susnerwala 2022), that have specified the details of the seizure definition used and who diagnosed the seizures, were scored 'some concerns'.

For the domain '**selection of reported results**', 11 trials (Gowda 2019; Jindal 2021; Pathak 2013; Perveen 2016; Saxena 2016; Sharpe 2020; Solanki 2015; Srinivasakumar 2015; Susnerwala 2022; Van Rooji 2010), had a low risk of bias as these trials were analysed as per *a priori* registered protocol, while seven trials (Akeel 2022; Boylan 2004; Falsaperla 2019; Ghaffar 2020; Khan 2020; Painter 1999; Prakash 2019), had some concerns as the trial protocols were not available for assessment.

The overall risk of bias of the included trials was as follows: one trial had a low risk of overall bias for all the outcomes (Soul 2021). 12 trials had a low risk for objective outcomes and some concerns or high risk for subjective outcomes (Akeel 2022; Gowda 2019; Jindal 2021; Pathak 2013; Perveen 2016; Prakash 2019; Saxena 2016; Sharpe 2020; Srinivasakumar 2015; Susnerwala 2022; Van Rooji 2010). Five trials had a high risk of overall bias for all the outcomes (Boylan 2004; Falsaperla 2019; Khan 2020; Painter 1999; Solanki 2015).

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures; **Summary of findings 2** Summary of findings table - Phenobarbital versus levetiracetam as first-line ASM for clinically diagnosed neonatal seizures; **Summary of findings 3** Summary of findings table - Phenobarbital versus phenytoin as first-line ASM for EEG-confirmed neonatal seizures; **Summary of findings 4** Summary of findings table - Phenobarbital versus phenytoin as first-line ASM for clinically diagnosed neonatal seizures; **Summary of findings 5** Summary of findings table - Phenobarbital versus Lorazepam as first-line ASM for clinically diagnosed neonatal seizures; **Summary of findings 6** Summary of findings table - Phenytoin versus lorazepam as first-line ASM for clinically diagnosed neonatal seizures; **Summary of findings 7** Summary of findings table - Phenobarbital + bumetanide versus phenobarbital alone for EEG-confirmed neonatal seizures; **Summary of findings 8** Summary of findings table - Lignocaine versus benzodiazepines as second-line ASM for EEG-confirmed neonatal seizures; **Summary of findings 9** Summary of findings table - Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures; **Summary of findings 10** Summary of findings table - Treatment of clinical and electrographic seizures versus treatment of clinical seizures alone in neonates

Comparison 1: Comparison of one ASM versus another

Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures

Please see Summary of findings 1.

Primary outcomes

Proportion of infants who achieve seizure control after first loading dose of ASM

As the dosage regimen of ASM was variable across the studies, we defined the first loading dose of ASM as 20 mg/kg for phenobarbital and 20 to 40 mg/kg for levetiracetam. We defined (post hoc) a time limit of 24 to 48 hours from the time of ASM administration to evaluate seizure control.

Data from one trial (Sharpe 2020) showed that phenobarbital probably results in better seizure control after the first loading dose of ASM compared to levetiracetam in EEG-confirmed neonatal seizures (RR 2.32, 95% CI 1.63 to 3.30; 106 participants; moderate-certainty evidence; Analysis 1.1).

Proportion of infants who achieve seizure control after maximal loading dose of ASM

The maximum loading dose of ASM was defined as 30 to 40 mg/kg for phenobarbital and 40 to 60 mg/kg for levetiracetam.

Data from one trial (Sharpe 2020), showed that phenobarbital probably results in better seizure control after the first loading dose of ASM compared to levetiracetam in EEG-confirmed neonatal seizures (RR 2.83, 95% CI 1.78 to 4.50; 83 participants; moderate-certainty evidence; Analysis 1.2).

Mortality or neurodevelopmental disability at 18 to 24 months' corrected age

The trial did not report this outcome (Sharpe 2020).

Secondary outcomes

Mortality before hospital discharge

Based on the data from one trial (Sharpe 2020), we are uncertain about the effect of using phenobarbital versus levetiracetam as first-line ASM on all-cause mortality before hospital discharge (RR 0.30, 95% CI 0.04 to 2.52; 106 participants; very low-certainty evidence; Analysis 1.3).

Neurodevelopmental disability at 18 to 24 months' corrected age

This outcome was not reported in the included study.

Proportion of infants who develop cognitive impairment at two years or more

This outcome was not reported in the included study.

Seizure burden (seizure hours per infant, or minutes per hour of monitoring) during hospitalisation

This outcome was not reported in the included study.

Proportion of infants with one or more of the adverse effects related to ASM(s) during hospitalisation

Requirement of mechanical ventilation

This outcome was reported in the one included trial (Sharpe 2020). We are uncertain about the effect of using phenobarbital versus levetiracetam as first-line ASM for the requirement of mechanical ventilation (RR 1.21, 95% CI 0.76 to 1.91; 106 participants; very low-certainty evidence; Analysis 1.4).

Proportion of infants who develop sedation or drowsiness

Based on data from the included trial (Sharpe 2020), we are uncertain about the effect of using phenobarbital versus levetiracetam as first-line ASM on the proportion of infants who develop sedation or drowsiness (RR 1.74, 95% CI 0.68 to 4.44; 106 participants; very low-certainty evidence; Analysis 1.5).

Arrhythmias causing circulatory disturbance

This outcome was not reported in the included study.

Bradycardia

Sharpe 2020 did not find a difference in the incidence of bradycardia between the two groups (RR 0.76, 95% CI 0.31 to 1.87; 106 participants; Analysis 1.6).

Hypotension requiring volume or inotropic support

The one included trial (Sharpe 2020) did not find a difference in hypotension between the phenobarbital and levetiracetam groups (RR 3.56, 95% CI 0.97 to 12.99; 106 participants; Analysis 1.7).

Shock requiring volume or inotropes

The one included trial (Sharpe 2020) did not find a difference in the incidence of shock between the two groups (RR 1.98, 99% CI 0.76 to 5.15; 106 participants; Analysis 1.8).

Hepatotoxicity resulting in discontinuation of therapy

This outcome was not reported in the included study.

Acute kidney injury (of any stage)

This outcome was not reported in the included study.

Proportion of infants with an abnormal background pattern in EEG during ASM treatment

This outcome was not reported in the included study.

Proportion of infants with an abnormal background pattern in EEG after ASM treatment

This outcome was not reported in the included study.

Duration of hospital stay (days)

This outcome was not reported in the included study.

Recurrence of seizures before hospital discharge

The one included trial (Sharpe 2020) did not find a difference in recurrence of seizures during hospital stay between the phenobarbital and levetiracetam groups (RR 1.33, 95% CI 0.52 to 3.40; 106 participants; Analysis 1.9).

Proportion of infants with persistent seizures or requiring ASM(s) at discharge (or both)

This outcome was not reported in the included study.

Proportion of infants discharged on gavage feeds

This outcome was not reported in the included study.

Proportion of infants with abnormal neurological examination at discharge

This outcome was not reported in the included study.

Proportion of infants who develop epilepsy post-discharge

Based on data from one trial (Sharpe 2020) we are uncertain about the effect of using phenobarbital versus levetiracetam as first-line ASM on the proportion of infants who develop epilepsy post-discharge (RR 0.92, 95% CI 0.48 to 1.76; 45 participants; very low-certainty evidence; Analysis 1.10).

Phenobarbital versus levetiracetam as first-line ASM for clinically diagnosed neonatal seizures

Please see Summary of findings 2.

Primary outcomes

Proportion of infants who achieve seizure control after the first loading dose of ASM

Three trials (Akeel 2022; Gowda 2019; Susnerwala 2022), have reported the outcome of seizure control until 24 to 48 hours after the first loading dose of ASM. We are uncertain about the effect of using phenobarbital versus levetiracetam as first-line ASM on achieving seizure control after the first loading dose in clinically-diagnosed seizures (RR 0.69, 95% CI 0.55 to 0.86; 286 participants; very low-certainty evidence; Analysis 2.1).

Proportion of infants who achieve seizure control after the maximal loading dose of ASM

Three trials (Ghaffar 2020; Gowda 2019; Khan 2020) reported this outcome. We are uncertain about the effect of using phenobarbital versus levetiracetam as first-line ASM on achieving seizure control after maximal loading dose of ASM in clinically-diagnosed seizures

(RR 0.58, 95% CI 0.47 to 0.72; 260 participants; very low-certainty evidence; Analysis 2.2).

Mortality or neurodevelopmental disability at 18 to 24 months' corrected age

This outcome was not reported in the eight included trials (Akeel 2022; Falsaperla 2019; Ghaffar 2020; Gowda 2019; Khan 2020; Perveen 2016; Prakash 2019; Susnerwala 2022).

Secondary outcomes

Mortality before hospital discharge

Six trials (Falsaperla 2019; Ghaffar 2020; Gowda 2019; Khan 2020; Prakash 2019; Susnerwala 2022) reported this outcome. Use of phenobarbital versus levetiracetam as first-line ASM may have little or no effect on all-cause mortality before hospital discharge (RR 1.41, 95% CI 0.82 to 2.43; 452 participants; low-certainty evidence; Analysis 2.3).

Neurodevelopmental disability at 18 to 24 months' corrected age

This outcome was not reported in the eight included trials.

Proportion of infants who develop cognitive impairment at two years or more

This outcome was not reported in the eight included trials.

Seizure burden (seizure hours per infant, or minutes per hour of monitoring) during hospitalisation

This outcome was not reported in the eight included trials.

Proportion of infants with one or more of the adverse effects related to ASM(s) during hospitalisation

Requirement for mechanical ventilation

The requirement for mechanical ventilation in trial participants was reported in five trials (Akeel 2022; Falsaperla 2019; Ghaffar 2020; Gowda 2019; Khan 2020). We are uncertain about the effect of using phenobarbital versus levetiracetam as first-line ASM on the need for mechanical ventilation (RR 2.20, 95% CI 0.50 to 9.68; 394 participants; very low-certainty evidence; Analysis 2.4).

Proportion of infants who develop sedation or drowsiness

Meta-analysis of two trials (Khan 2020; Prakash 2019) showed no difference in sedation/drowsiness between the two groups (RR 1.88, 95% CI 0.66 to 5.37; 180 participants; very low-certainty evidence; Analysis 2.5).

Arrhythmias causing circulatory disturbance

This outcome was not reported in the eight included trials.

Bradycardia

Meta-analysis of four trials (Akeel 2022; Falsaperla 2019; Gowda 2019; Khan 2020) showed no difference in the incidence of bradycardia between phenobarbital and levetiracetam groups (RR 6.00, 95% CI 0.74 to 48.97; 334 participants; Analysis 2.6).

Hypotension requiring volume or inotropic support

Two trials (Falsaperla 2019; Khan 2020) reported this outcome. None of the infants in either study had hypotension requiring volume or inotropic support (Analysis 2.7).

Shock requiring volume or inotropes

Meta-analysis of three trials (Falsaperla 2019; Khan 2020; Perveen 2016) showed no difference in the risk of shock between phenobarbital and levetiracetam groups (RR 0.67, 99% CI 0.30 to 1.51; 190 participants; Analysis 2.8).

Hepatotoxicity resulting in discontinuation of therapy

This outcome was not reported in the eight included trials.

Acute kidney injury (of any stage)

This outcome was not reported in the eight included trials.

Proportion of infants with an abnormal background pattern in EEG during ASM treatment

One trial (Falsaperla 2019), did not find a difference in the proportion of infants with an abnormal background pattern in EEG during ASM treatment between phenobarbital and levetiracetam groups (RR 1.00, 95% CI 0.88 to 1.13; 30 participants; Analysis 2.9).

Proportion of infants with an abnormal background pattern in EEG after stopping ASM treatment

One trial (Falsaperla 2019), did not find a difference in the proportion of infants with an abnormal background pattern in EEG after the ASM treatment between phenobarbital and levetiracetam groups (RR 0.63, 95% CI 0.26 to 1.47; 30 participants; Analysis 2.10).

Duration of hospital stay (days)

Meta-analysis of two trials (Falsaperla 2019; Perveen 2016) showed an increase in the duration of hospital stay in the phenobarbital group compared to the levetiracetam group (MD 2.36 days, 95% CI 0.54 to 4.18; 90 participants; Analysis 2.11).

Recurrence of seizures before hospital discharge

Meta-analysis of two trials (Falsaperla 2019; Khan 2020) showed no difference in recurrence of seizures during hospital stay between phenobarbital and levetiracetam groups (RR 1.67, 95% CI 0.42 to 6.60; 130 participants; Analysis 2.12).

Proportion of infants with persistent seizures or requiring ASM(s) at discharge (or both)

One trial (Falsaperla 2019) did not find a difference in the proportion of infants with persistent seizures or requiring ASM at discharge (RR 0.50, 95% CI 0.05 to 4.94; 30 participants; Analysis 2.13).

Proportion of infants discharged on gavage feeds

Two trials (Falsaperla 2019; Khan 2020) reported this outcome. None of the babies in either group was discharged on gavage feeds (Analysis 2.14).

Proportion of infants with an abnormal neurological examination at discharge

Meta-analysis of four trials (Falsaperla 2019; Khan 2020; Perveen 2016; Susnerwala 2022), showed no difference in the proportion of infants with an abnormal neurological examination at discharge

between phenobarbital and levetiracetam groups (RR 0.80, 95% CI 0.51 to 1.24; 272 participants; Analysis 2.15).

Proportion of infants who develop epilepsy post-discharge

One trial (Falsaperla 2019) has reported this outcome. We are uncertain about the effect of using phenobarbital versus levetiracetam as first-line ASM on achieving seizure control after the first loading dose in clinically-diagnosed seizures (RR 0.50, 95% CI 0.05 to 4.9; 30 participants; very low-certainty evidence; Analysis 2.16).

Phenobarbital versus phenytoin as first-line ASM for EEG-confirmed neonatal seizures

Please see Summary of findings 3.

Primary outcomes

Proportion of infants who achieve seizure control after first loading dose of ASM

The one included trial did not report this outcome (Painter 1999).

Proportion of infants who achieve seizure control after the maximal loading dose of ASM

One trial (Painter 1999) has reported this outcome. We are uncertain about the effect of using phenobarbital versus phenytoin as first-line ASM on achieving seizure control after the maximal dose of ASM in EEG-confirmed neonatal seizures (RR 0.97, 95% CI 0.54 to 1.72; 59 participants; very low-certainty evidence).

Mortality or neurodevelopmental disability at 18 to 24 months' corrected age

The one included trial did not report this outcome.

Secondary outcomes

Mortality before hospital discharge

The one included trial did not report this outcome.

Neurodevelopmental disability at 18 to 24 months' corrected age

The one included trial did not report this outcome.

Proportion of infants who develop cognitive impairment at two years or more

The one included trial did not report this outcome.

Seizure burden during hospitalisation

The one included trial did not report this outcome.

Proportion of infants with one or more of the adverse effects related to ASM(s) during hospitalisation

Requirement for mechanical ventilation

The one included trial did not report this outcome.

Proportion of infants who develop sedation or drowsiness

The one included trial did not report this outcome.

Arrhythmias causing circulatory disturbance

The one included trial (Painter 1999) reported this outcome. None of the babies in either group developed any arrythmia in this trial (Analysis 3.2).

Bradycardia

The one included trial (Painter 1999) reported this outcome. None of the babies in either group developed bradycardia in this trial (Analysis 3.3).

Hypotension requiring volume or inotropic support

The one included trial (Painter 1999) reported this outcome. None of the babies in either group developed hypotension in this trial (Analysis 3.4).

Shock requiring volume or inotropes

The one included trial did not report this outcome.

Hepatotoxicity resulting in discontinuation of therapy

The one included trial did not report this outcome.

Acute kidney injury (of any stage)

The one included trial did not report this outcome.

Proportion of infants with an abnormal background pattern in EEG during ASM treatment

The one included trial did not report this outcome.

Proportion of infants with an abnormal background pattern in EEG after stopping the ASM

The one included trial did not report this outcome.

Duration of hospital stay (days)

The one included trial did not report this outcome.

Proportion of infants with persistent seizures or requiring ASM(s) at discharge (or both)

The one included trial did not report this outcome.

Proportion of infants discharged on gavage feeds

The one included trial did not report this outcome.

Proportion of infants with abnormal neurological examination at discharge

The one included trial did not report this outcome.

Proportion of infants who develop epilepsy post-discharge

The one included trial did not report this outcome.

Phenobarbital versus phenytoin as first-line ASM for clinically diagnosed neonatal seizures

Please see Summary of findings 4.

Primary outcomes

Proportion of infants who achieve seizure control after the first loading dose of ASM

Both included trials (Pathak 2013; Solanki 2015) reported this outcome. Using phenobarbital may result in better seizure control

after the first loading dose of ASM when compared to phenytoin in clinically diagnosed seizures (RR 1.92, 95% CI 1.40 to 2.64; 179 participants; low-certainty evidence; Analysis 4.1).

Proportion of infants who achieve seizure control after the maximal loading dose of ASM

Neither of the two included trials reported this outcome.

Mortality or neurodevelopmental disability at 18 to 24 months' corrected age

Neither of the two included studies reported this outcome.

Secondary outcomes

Mortality before hospital discharge

Both included trials (Pathak 2013; Solanki 2015) reported this outcome. We are uncertain about the effect of using phenobarbital versus phenytoin as first-line ASM on all-cause mortality before hospital discharge (RR 1.33, 95% CI 0.79 to 2.26; 179 participants; very low-certainty evidence; Analysis 4.2).

Neurodevelopmental disability at 18 to 24 months' corrected age

Neither of the two included studies reported this outcome.

Proportion of infants who develop cognitive impairment at two years or more

Neither of the two included studies reported this outcome.

Seizure burden during hospitalisation

Neither of the two included studies reported this outcome.

Proportion of infants with one or more of the adverse effects related to ASM(s) during hospitalisation

Requirement for mechanical ventilation

One trial (Pathak 2013) reported on the need for mechanical ventilation. We are uncertain about the effect of using phenobarbital versus phenytoin as first-line ASM on the need for mechanical ventilation (RR 7.13, 95% CI 0.38 to 134.78; 109 participants; very low-certainty evidence; Analysis 4.3).

Proportion of infants with sedation or drowsiness

Based on data from one trial (Solanki 2015), we are uncertain about the effect of using phenobarbital versus phenytoin as first-line ASM on the risk of sedation or drowsiness (RR 23.00, 95% CI 1.41 to 375.77; 70 participants; very low-certainty evidence; Analysis 4.4).

Arrhythmias causing circulatory disturbance

Neither of the two included studies reported this outcome.

Bradycardia

One trial (Pathak 2013), did not find a difference in the proportion of infants with bradycardia between the groups (RR 0.20, 95% CI 0.01 to 4.15; Analysis 4.5).

Hypotension requiring volume or inotropic support

Neither of the two included studies reported this outcome.

Shock requiring volume or inotropes

Neither of the two included studies reported this outcome.

Hepatotoxicity resulting in discontinuation of therapy

Neither of the two included studies reported this outcome.

Acute kidney injury (of any stage)

Neither of the two included studies reported this outcome.

Proportion of infants with an abnormal background pattern in EEG during ASM treatment

Neither of the two included studies reported this outcome.

Proportion of infants with an abnormal background pattern in EEG after stopping ASM

Neither of the two included studies reported this outcome.

Duration of hospital stay (days)

Neither of the two included studies reported this outcome.

Proportion of infants with persistent seizures or requiring ASM(s) at discharge (or both)

One trial (Solanki 2015) did not find a difference in the proportion of infants with persistent seizures or requiring ASM at discharge between the phenobarbital and phenytoin groups (RR 0.67, 95% CI 0.21 to 2.16; 70 participants; Analysis 4.6).

Proportion of infants discharged on gavage feeds

Neither of the two included studies reported this outcome.

Proportion of infants with an abnormal neurological examination at discharge

Neither of the two included studies reported this outcome.

Proportion of infants who develop epilepsy post-discharge

Neither of the two included studies reported this outcome.

Phenobarbital versus lorazepam as first-line ASM for clinically diagnosed neonatal seizures

Please see Summary of findings 5.

Primary outcomes

Proportion of infants who achieve seizure control after the first loading dose of ASM

The one included trial (Solanki 2015) reported this outcome. We are uncertain about the effect of phenobarbital compared to lorazepam on seizure control after the first loading dose of ASM (RR 0.71, 95% CI 0.53 to 0.94; 71 participants; very low-certainty evidence; Analysis 5.1).

Proportion of infants who achieve seizure control after the maximal loading dose of ASM

The one included trial did not report this outcome (Solanki 2015).

Mortality or neurodevelopmental disability at 18 to 24 months' corrected age

The one included trial did not report this outcome.

Secondary outcomes

Mortality before hospital discharge

The one included trial (Solanki 2015) reported this outcome. We are uncertain about the effect of phenobarbital compared to lorazepam on mortality before discharge (RR 1.76, 95% CI 0.79 to 3.95; 71 participants; very low-certainty evidence; Analysis 5.2).

Neurodevelopmental disability at 18 to 24 months' corrected age

The one included trial did not report this outcome.

Proportion of infants who develop cognitive impairment at two years or more

The one included trial did not report this outcome.

Seizure burden during hospitalisation

The one included trial did not report this outcome.

Proportion of infants with one or more of the adverse effects related to ASM(s) during hospitalisation

Requirement for mechanical ventilation

The one included trial did not report this outcome.

Proportion of infants who develop sedation or drowsiness

The one included trial (Solanki 2015) reported this outcome. We are uncertain about the effect of phenobarbital compared to lorazepam on sedation or drowsiness (RR 5.66, 95% CI 1.35 to 23.71; 71 participants; very low-certainty evidence; Analysis 5.3).

Arrhythmias causing circulatory disturbance

The one included trial did not report this outcome.

Bradycardia

The one included trial did not report this outcome.

Hypotension requiring volume or inotropic support

The one included trial did not report this outcome.

Shock requiring volume or inotropes

The one included trial did not report this outcome.

Hepatotoxicity resulting in discontinuation of therapy

The one included trial did not report this outcome.

Acute kidney injury (of any stage)

The one included trial did not report this outcome.

Proportion of infants with an abnormal background pattern in EEG during ASM treatment

The one included trial did not report this outcome.

Proportion of infants with an abnormal background pattern in EEG after stopping ASM

The one included trial did not report this outcome.

Duration of hospital stay (days)

The one included trial did not report this outcome.

Proportion of infants with persistent seizures or requiring ASM(s) at discharge

The one included trial (Solanki 2015) did not find a difference in the proportion of infants with persistent seizures or requiring ASM at discharge between the phenobarbital and lorazepam groups (RR 9.25, 95% CI 0.52 to 165.69; 71 participants; Analysis 5.4).

Proportion of infants discharged on gavage feeds

The one included trial did not report this outcome.

Proportion of infants with an abnormal neurological examination at discharge

The one included trial did not report this outcome.

Proportion of infants who develop epilepsy post-discharge

The one included trial did not report this outcome.

Phenytoin versus lorazepam as first-line ASM for clinically diagnosed neonatal seizures

Please see Summary of findings 6.

Primary outcomes

Proportion of infants who achieve seizure control after the first loading dose of ASM

The one included trial (Solanki 2015) reported this outcome. We are uncertain about the effect of phenytoin compared to lorazepam on seizure control after the first loading dose of ASM (RR 0.77, 95% CI 0.60 to 0.99; 71 participants; very low-certainty evidence; Analysis 6.1).

Proportion of infants who achieve seizure control after the maximal loading dose of ASM

The one included trial did not report this outcome.

Mortality or neurodevelopmental disability at 18 to 24 months' corrected age

The one included trial did not report this outcome.

Secondary outcomes

Mortality before hospital discharge

The one included trial (Solanki 2015) reported this outcome. We are uncertain about the effect of phenytoin compared to lorazepam on mortality before discharge (RR 0.44, 95% CI 0.12 to 1.57; 71 participants; very low-certainty evidence; Analysis 6.2).

Neurodevelopmental disability at 18 to 24 months' corrected age

The one included trial did not report this outcome.

Proportion of infants who develop cognitive impairment at two years or more

The one included trial did not report this outcome.

Seizure burden during hospitalisation

The one included trial did not report this outcome.

Proportion of infants with one or more of the adverse effects related to ASM(s) during hospitalisation

Requirement for mechanical ventilation

The one included trial did not report this outcome.

Proportion of infants who develop sedation or drowsiness

The one included trial (Solanki 2015) reported this outcome. We are uncertain about the effect of phenobarbital compared to lorazepam on sedation or drowsiness (RR 0.21, 95% CI 0.01 to 4.13; 71 participants; very low-certainty evidence; Analysis 6.3).

Arrhythmias causing circulatory disturbance

The one included trial did not report this outcome.

Bradycardia

The one included trial did not report this outcome.

Hypotension requiring volume or inotropic support

The one included trial did not report this outcome.

Shock requiring volume or inotropes

The one included trial did not report this outcome.

Hepatotoxicity resulting in discontinuation of therapy

The one included trial did not report this outcome.

Acute kidney injury (of any stage)

The one included trial did not report this outcome.

Proportion of infants with an abnormal background pattern in EEG during ASM treatment

The one included trial did not report this outcome.

Proportion of infants with an abnormal background pattern in EEG after stopping the ASM

The one included trial did not report this outcome.

Duration of hospital stay (days)

The one included trial did not report this outcome.

Proportion of infants with persistent seizures or requiring ASM(s) at discharge

The one included trial (Solanki 2015) did not find a difference in the proportion of infants with persistent seizures or requiring ASM at discharge between the phenytoin and lorazepam groups (RR 13.36, 95% CI 0.78 to 228.6; 71 participants; Analysis 6.4).

Proportion of infants discharged on gavage feeds

The one included trial did not report this outcome.

Proportion of infants with an abnormal neurological examination at discharge

The one included trial did not report this outcome.

Proportion of infants who develop epilepsy post-discharge

The one included trial did not report this outcome.

Phenobarbital + bumetanide versus phenobarbital alone as first-line ASM for EEG-confirmed neonatal seizures

Please see Summary of findings 7.

Primary outcomes

Proportion of infants who achieve seizure control after the first loading dose of ASM

The one included trial (Soul 2021) reported this outcome. Phenobarbital + bumetanide when compared to phenobarbital alone may have little or no effect on seizure control after the first loading dose of ASM (RR 0.95, 95% CI 0.37 to 2.40; 43 participants; low-certainty evidence; Analysis 7.1).

Proportion of infants who achieve seizure control after the maximal loading dose of ASM

The one included trial did not report this outcome.

Mortality or neurodevelopmental disability at 18 to 24 months' corrected age

The one included trial did not report this outcome.

Secondary outcomes

Mortality before hospital discharge

The one included trial (Soul 2021) reported this outcome. We are uncertain about the effect of phenobarbital + bumetanide when compared to phenobarbital alone on all-cause mortality before hospital discharge (RR 0.20, 95% CI 0.02 to 1.74; 43 participants; very low-certainty evidence; Analysis 7.2).

Neurodevelopmental disability at 18 to 24 months' corrected age

The one included trial did not report this outcome.

Proportion of infants who develop cognitive impairment at two years or more

The one included trial (Soul 2021) reported cognitive impairment at 18 to 24 months. We are uncertain about the effect of phenobarbital + bumetanide when compared to phenobarbital alone on all-cause mortality before hospital discharge (RR 0.53, 95% CI 0.13 to 2.15; 43 participants; very low-certainty evidence; Analysis 7.3).

Seizure burden during hospitalisation

The one included trial did not find a difference in seizure burden between the two groups (MD 1.90, 95% CI 0.52 to 3.28; 43 participants; Analysis 7.4).

Proportion of infants with one or more of the adverse effects related to ASM(s) during hospitalisation

Requirement for mechanical ventilation

In the one included trial (Soul 2021), none of the babies in either group required mechanical ventilation (Analysis 7.5).

Proportion of infants who develop sedation or drowsiness

The one included trial did not report this outcome.

Arrhythmias causing circulatory disturbance

The one included trial did not report this outcome.

Bradycardia

The one included trial did not report this outcome.

Hypotension requiring volume or inotropic support

In the one included trial (Soul 2021), none of the babies in either group developed hypotension (Analysis 7.6).

Shock requiring volume or inotropes

The one included trial did not report this outcome.

Hepatotoxicity resulting in discontinuation of therapy

The one included trial did not report this outcome.

Acute kidney injury (of any stage)

The one included trial did not report this outcome.

Proportion of infants with an abnormal background pattern in EEG during ASM treatment

The one included trial (Soul 2021) found no difference in the proportion of infants with an abnormal background pattern in EEG during ASM treatment between phenobarbital + bumetanide and phenobarbital alone groups (RR 1.05, 95% CI 0.62 to 1.80; 43 participants; Analysis 7.7).

Proportion of infants with an abnormal background pattern in EEG after stopping ASM

The one included trial did not report this outcome.

Duration of hospital stay (days)

The one included trial did not report this outcome.

Proportion of infants with persistent seizures or requiring ASM(s) at discharge

The one included trial did not report this outcome.

Proportion of infants discharged on gavage feeds

The one included trial did not report this outcome.

Proportion of infants with an abnormal neurological examination at discharge

The one included trial did not report this outcome.

Proportion of infants who developed epilepsy post-discharge

The one included trial (Soul 2021) reported this outcome. We are uncertain about the effect of phenobarbital + bumetanide when compared to phenobarbital alone on the proportion of infants who developed epilepsy post-discharge (RR 1.13, 95% CI 0.43 to 2.97; 39 participants; very low-certainty evidence; Analysis 7.8).

Lignocaine versus benzodiazepines as second-line ASM for EEG-confirmed neonatal seizures

Please see Summary of findings 8.

Primary outcomes

Proportion of infants who achieve seizure control after the first loading dose of ASM

The one included trial did not report this outcome (Boylan 2004).

Proportion of infants who achieve seizure control after the maximal loading dose of ASM

The one included trial (Boylan 2004) reported this outcome. We are uncertain about the effect of lignocaine when compared to benzodiazepines as second-line ASM on achieving seizure control after maximal loading dose of ASM (RR 8.17, 95% CI 0.52 to 128.42; 11 participants; very low-certainty evidence; Analysis 8.1).

Mortality or neurodevelopmental disability at 12 months' corrected age

The one included trial (Boylan 2004) reported this outcome. We are uncertain about the effect of lignocaine when compared to benzodiazepines as second-line ASM on mortality or neurodevelopmental disability at 18 to 24 months' corrected age (RR 1.00, 95% CI 0.71 to 1.41; 10 participants; very low-certainty evidence; Analysis 8.2).

Secondary outcomes

Mortality before hospital discharge

The one included trial (Boylan 2004) reported this outcome. We are uncertain about the effect of lignocaine when compared to benzodiazepines as second-line ASM on all-cause mortality before discharge (RR 1.20, 95% CI 0.25 to 5.71; 11 participants; very low-certainty evidence; Analysis 8.3).

Neurodevelopmental disability at 12 months' corrected age

The one included trial (Boylan 2004) reported this outcome. We are uncertain about the effect of lignocaine when compared to benzodiazepines as second-line ASM on mortality or neurodevelopmental disability at 18 to 24 months' corrected age (RR 1.00, 95% CI 0.36 to 2.75; 10 participants; very low-certainty evidence; Analysis 8.4).

Proportion of infants who develop cognitive impairment at two years or more

The one included trial did not report this outcome.

Seizure burden during hospitalisation

The one included trial did not report this outcome.

Proportion of infants with one or more of the adverse effects related to ASM(s) during hospitalisation

Requirement of mechanical ventilation

The one included trial did not report this outcome.

Proportion of infants who develop sedation or drowsiness

The one included trial did not report this outcome.

Arrhythmias causing circulatory disturbance

The one included trial did not report this outcome.

Bradycardia

The one included trial did not report this outcome.

Hypotension requiring volume or inotropic support

The one included trial did not report this outcome.

Shock requiring volume or inotropes

The one included trial did not report this outcome.

Hepatotoxicity resulting in discontinuation of therapy

The one included trial did not report this outcome.

Acute kidney injury (of any stage)

The one included trial did not report this outcome.

Proportion of infants with an abnormal background pattern in EEG during ASM treatment

The one included trial did not report this outcome.

Proportion of infants with an abnormal background pattern in EEG after stopping ASM

The one included trial did not report this outcome.

Duration of hospital stay (days)

The one included trial did not report this outcome.

Proportion of infants with persistent seizures or requiring ASM(s) at discharge

The one included trial did not report this outcome.

Proportion of infants discharged on gavage feeds

The one included trial did not report this outcome.

Proportion of infants with an abnormal neurological examination at discharge

The one included trial did not report this outcome.

Proportion of infants who develop epilepsy post-discharge

The one included trial did not report this outcome.

Comparison 2: Maintenance therapy with ASM versus no maintenance therapy after achieving seizure control for clinically diagnosed neonatal seizures

Please see Summary of findings 9.

Primary outcomes

Proportion of infants who achieve seizure control after a single or maximal dose of the given ASM

These outcomes are not relevant to this comparison.

Proportion of infants with repeat seizures before hospital discharge

The 'proportion of infants who achieve seizure control' was evaluated using the outcome 'proportion of infants who developed repeated seizures during hospitalisation'. Both included trials (Jindal 2021; Saxena 2016) reported this outcome. We are uncertain about the effect of maintenance therapy with ASM compared to no maintenance therapy after achieving seizure control on the incidence of recurrent seizures before hospital discharge (RR 0.76, 95% CI 0.56 to 1.01; 373 participants; very-low certainty evidence; Analysis 9.1).

Mortality or neurodevelopmental disability at 18 to 24 months' corrected age

Neither of the two included studies reported this outcome.

Secondary outcomes

Mortality before hospital discharge

Both trials (Jindal 2021; Saxena 2016) reported this outcome. Maintenance therapy with ASM compared to no maintenance therapy may have little or no effect on all-cause mortality before hospital discharge (RR 0.69, 95% CI 0.39 to 1.22; 373 participants; low-certainty evidence; Analysis 9.2).

Mortality at 18 to 24 months

One trial (Saxena 2016) reported this outcome. Maintenance therapy with ASM compared to no maintenance therapy may have little or no effect on mortality at 18 to 24 months (RR 0.94, 95% CI 0.34 to 2.61; 111 participants; low-certainty evidence; Analysis 9.3).

Neurodevelopmental disability at 18 to 24 months' corrected age

One trial (Saxena 2016) reported this outcome. Maintenance therapy with ASM compared to no maintenance therapy may have little or no effect on neurodevelopmental disability at 18 to 24 months (RR 0.89, 95% CI 0.13 to 6.12; 108 participants; low-certainty evidence; Analysis 9.4).

Proportion of infants who develop cognitive impairment at two years or more

Neither of the two included studies reported this outcome.

Seizure burden during hospitalisation

Neither of the two included studies reported this outcome.

Proportion of infants with one or more of the adverse effects related to ASM(s) during hospitalisation

Requirement for mechanical ventilation

Data from one trial (Jindal 2021) showed no difference in the requirement of mechanical ventilation between the two groups (RR 0.83, 95% CI 0.63 to 1.10; 221 participants; Analysis 9.5).

Proportion of infants with sedation or drowsiness

Neither of the two trials reported this outcome.

Arrhythmias causing circulatory disturbance

Neither of the two included studies reported this outcome.

Bradycardia

Neither of the two included studies reported this outcome.

Hypotension requiring volume or inotropic support

Neither of the two included studies reported this outcome.

Shock requiring volume or inotropes

Meta-analysis of data from both trials (Jindal 2021; Saxena 2016) did not show a difference in the need for inotropes between the two groups (RR 0.84, 95% CI 0.67 to 1.07; 373 participants; Analysis 9.6).

Hepatotoxicity resulting in discontinuation of therapy

Neither of the two included studies reported this outcome.

Acute kidney injury (of any stage)

Neither of the two included studies reported this outcome.

Proportion of infants with an abnormal background pattern in EEG during ASM treatment

Neither of the two included studies reported this outcome.

Proportion of infants with an abnormal background pattern in EEG after achieving seizure control

Data from one trial (Saxena 2016) showed no difference in the proportion of infants with an abnormal background pattern in EEG after achieving seizure control between maintenance therapy with ASM and no maintenance therapy groups (RR 0.76, 95% CI 0.30 to 1.97; 118 participants; Analysis 9.7).

Duration of hospital stay (days)

Meta-analysis of data from both trials (Jindal 2021; Saxena 2016) did not show a difference in the duration of hospital stay between maintenance therapy with ASM and no maintenance therapy groups (MD 0.13, 95% CI -0.44 to 0.70; 373 participants; Analysis 9.8).

Proportion of infants with persistent seizures or requiring ASM(s) at discharge

Data from one trial (Jindal 2021), showed no difference in the proportion of infants with persistent seizures or requiring ASM(s) at discharge between the two groups (RR 1.33, 95% CI 0.98 to 1.80; 221 participants; Analysis 9.9).

Proportion of infants discharged on gavage feeds

Neither of the two included studies reported this outcome.

Proportion of infants with an abnormal neurological examination at discharge

Meta-analysis of data from both trials (Jindal 2021; Saxena 2016) did not show a difference in the proportion of infants with an abnormal neurological examination at discharge between the two groups (RR 0.88, 95% CI 0.62 to 1.26; 373 participants; Analysis 9.10).

Proportion of infants who develop epilepsy post-discharge

One trial (Saxena 2016) reported this outcome. Maintenance therapy with ASM compared to no maintenance therapy may have little or no effect on the proportion of infants who develop epilepsy post-discharge (RR 3.18, 95% CI 0.69 to 14.72; 126 participants; low certainty evidence; Analysis 9.11).

Comparison 3: Treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates

Please see Summary of findings 10.

Primary outcomes

Proportion of infants who achieve seizure control after the first or maximal dose of the given ASM

This outcome is not relevant to this comparison.

Seizure burden during hospitalisation

The 'proportion of infants who achieve seizure control' was evaluated using the outcome 'seizure burden'. (See Differences between protocol and review).

Both trials (Srinivasakumar 2015; Van Rooji 2010) reported this outcome. Treatment of both clinical and electrographic seizures when compared to treatment of clinical seizures alone may have little or no effect on all-cause mortality before hospital discharge (MD -1871.16, 95% CI -4525.05 to 782.73; 68 participants; low-certainty evidence; Analysis 10.1).

Mortality or neurodevelopmental disability at 18 to 24 months' corrected age

Neither of the two trials (Srinivasakumar 2015; Van Rooji 2010) that compared ASM treatment for only-electrographic seizures versus no ASM treatment reported this outcome.

Secondary outcomes

Mortality before hospital discharge

Both trials (Srinivasakumar 2015; Van Rooji 2010) reported this outcome. Treatment of both clinical and electrographic seizures when compared to treatment of clinical seizures alone may have little or no effect on all-cause mortality before hospital discharge (RR 0.59, 95% CI 0.28 to 1.27; 68 participants; low-certainty evidence; Analysis 10.2).

Neurodevelopmental disability at 18 to 24 months corrected age

Neither of the two trials reported this outcome.

Proportion of infants who develop cognitive impairment at two years or more

Neither of the two trials reported this outcome.

Proportion of infants with one or more of the adverse effects related to ASM(s) during hospitalisation

Requirement for mechanical ventilation

Neither of the two trials reported this outcome.

Proportion of infants with sedation or drowsiness

Neither of the two trials reported this outcome.

Arrhythmias causing circulatory disturbance

Neither of the two trials reported this outcome.

Bradycardia

Neither of the two trials reported this outcome.

Hypotension requiring volume or inotropic support

Neither of the two trials reported this outcome.

Shock requiring volume or inotropes

Neither of the two trials reported this outcome.

Hepatotoxicity resulting in discontinuation of therapy

Neither of the two trials reported this outcome.

Acute kidney injury (of any stage)

Neither of the two trials reported this outcome.

Proportion of infants with an abnormal background pattern in EEG during ASM treatment

Neither of the two trials reported this outcome.

Proportion of infants with an abnormal background pattern in EEG after stopping the ASM

Neither of the two trials reported this outcome.

Duration of hospital stay (days)

Neither of the two trials reported this outcome.

Proportion of infants with persistent seizures or requiring ASM(s) at discharge

Neither of the two trials reported this outcome.

Proportion of infants discharged on gavage feeds

Neither of the two trials reported this outcome.

Proportion of infants with an abnormal neurological examination at discharge

Neither of the two trials reported this outcome.

Proportion of infants who develop epilepsy post-discharge

One trial (Srinivasakumar 2015) reported this outcome. Treatment of both clinical and electrographic seizures when compared to treatment of clinical seizures alone may have little or no effect on the proportion of infants who developed epilepsy post-discharge between the two groups (RR 0.75, 95% CI 0.12 to 4.73; 35 participants; low-certainty evidence; Analysis 10.3).

DISCUSSION

Summary of main results

We included a total of 18 trials (1342 infants) in this systematic review.

We included 14 trials for the comparison of one ASM versus an alternative ASM for the treatment of neonatal seizures (Akeel 2022; Boylan 2004; Falsaperla 2019; Ghaffar 2020; Gowda 2019; Khan 2020; Painter 1999; Pathak 2013; Perveen 2016; Prakash 2019; Sharpe 2020; Solanki 2015; Soul 2021; Susnerwala 2022). Amongst these, nine trials (Akeel 2022; Falsaperla 2019; Ghaffar 2020; Gowda 2019; Khan 2020; Perveen 2016; Prakash 2019; Sharpe 2020; Susnerwala 2022) compared phenobarbital versus levetiracetam as first-line ASM; two trials (Painter 1999; Pathak 2013) compared phenobarbital versus phenytoin as first-line ASM; one three-armed trial (Solanki 2015) compared phenobarbital versus phenytoin versus lorazepam as first-line ASM; one trial (Soul 2021) compared phenobarbital+bumetanide versus phenobarbital alone and one trial (Boylan 2004), compared lignocaine versus benzodiazepines as second-line ASM.

One trial (Sharpe 2020) compared phenobarbital versus levetiracetam as first-line ASM in EEG-confirmed neonatal seizures. Phenobarbital is probably more effective than levetiracetam in achieving seizure control after the first loading dose (RR 2.32, 95% CI 1.63 to 3.30; 106 participants; moderate-certainty evidence). Similarly, phenobarbital is probably more effective than levetiracetam in achieving seizure control after the maximal loading dose (RR 2.83, 95% CI 1.78 to 4.50; 106 participants; moderate-certainty evidence). However, we are uncertain about the effect of phenobarbital when compared to levetiracetam on other outcomes such as mortality before hospital discharge (RR 0.30, 95% CI 0.04 to 2.52; 106 participants; very low-certainty evidence); the requirement for mechanical ventilation (RR 1.21, 95% CI 0.76 to 1.91; 106 participants; very low-certainty evidence); sedation or drowsiness (RR 1.74, 95% CI 0.68 to 4.44; 106 participants; very low-certainty evidence); and proportion of infants with epilepsy post-discharge (RR 0.92, 95% CI 0.48 to 1.76; 106 participants; very low-certainty evidence). We did not find any data on the impact of phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed seizures on important long-term outcomes such as mortality or neurodevelopmental disability at 18 to 24 months or on cognitive impairment at two years or more.

Eight trials (Akeel 2022; Falsaperla 2019; Ghaffar 2020; Gowda 2019; Khan 2020; Perveen 2016; Prakash 2019; Susnerwala 2022) compared phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures. We are uncertain about the efficacy of phenobarbital versus levetiracetam in achieving seizure control after the first loading dose (RR 0.69, 95% CI 0.55 to 0.86; 286 participants; very low-certainty evidence), and seizure control after the maximal loading dose (RR 0.58, 95% CI 0.47 to 0.72; 260 participants; very low-certainty evidence). Use of phenobarbital versus levetiracetam as first-line ASM may have little or no effect on all-cause mortality before discharge (RR 1.41, 95% CI 0.82 to 2.43; 452 participants; low-certainty evidence). We are also uncertain regarding the effect of phenobarbital versus levetiracetam as first-line ASM on other important outcomes such as requirement for mechanical ventilation (RR 2.20, 95% CI 0.50 to 9.68; 394 participants; very low-certainty evidence); sedation or drowsiness (RR 1.88, 95% CI 0.66 to 5.37; 180 participants; very low-certainty evidence); and proportion of infants with epilepsy post-discharge (RR 0.50, 95% CI 0.05 to 4.94; 30 participants; very low-certainty evidence). There were no data on important long-term outcomes such as mortality or neurodevelopmental disability at 18 to 24 months or on cognitive impairment at two years or more.

One trial (Painter 1999) compared phenobarbital versus phenytoin as first-line ASM in EEG-confirmed neonatal seizures. We are uncertain about the effect of phenobarbital versus phenytoin on achieving seizure control after the maximal dose (RR 0.97, 95% CI 0.54 to 1.72; 59 participants; very low-certainty evidence). We did not find any data on the impact of phenobarbital versus phenytoin as first-line ASM for EEG-confirmed seizures on seizure control after the maximal loading dose, mortality before hospital discharge, risk of various adverse effects due to ASM, proportion of infants who develop epilepsy post-discharge and on important long-term outcomes such as mortality or neurodevelopmental disability at 18 to 24 months or on cognitive impairment at two years or more.

Two trials (Pathak 2013; Solanki 2015) compared phenobarbital versus phenytoin as first-line ASM in clinically diagnosed neonatal seizures. Phenobarbital may be more effective than phenytoin in achieving seizure control after the first loading dose (RR 1.92, 95% CI 1.40 to 2.64; 179 participants; low-certainty evidence). We are uncertain regarding the effect of phenobarbital when compared to phenytoin on other outcomes such as mortality before hospital discharge (RR 1.33, 95% CI 0.79 to 2.26; 179 participants; very low-certainty evidence); requirement for mechanical ventilation (RR 7.13, 95% CI 0.38 to 134.78; 109 participants; very low-certainty evidence); and sedation or drowsiness (RR 23.00, 95% CI 1.41 to 375.77; 70 participants; very low-certainty evidence). We did not

find any data on the impact of phenobarbital versus phenytoin as first-line ASM for clinically diagnosed seizures on seizure control after the maximal loading dose of ASM and on important long-term outcomes such as mortality or neurodevelopmental disability at 18 to 24 months or on cognitive impairment at two years or more.

One trial (Solanki 2015) compared phenobarbital versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures. We are uncertain as to the effect of phenobarbital versus lorazepam on achieving seizure control after the first loading dose (RR 0.71, 95% CI 0.53 to 0.94; 71 participants; very low-certainty evidence); mortality before hospital discharge (RR 1.76, 95% CI 0.79 to 3.95; 71 participants; very low-certainty evidence); and sedation or drowsiness (RR 5.66, 95% CI 1.35 to 23.71; 71 participants; very low-certainty evidence). We did not find any data on the impact of phenobarbital versus lorazepam as first-line ASM for clinically diagnosed seizures on seizure control after the maximal loading dose of ASM, risk of various adverse effects due to ASM, proportion of infants who develop epilepsy post-discharge and on important long-term outcomes such as mortality or neurodevelopmental disability at 18 to 24 months or cognitive impairment at two years or more.

One trial (Solanki 2015) compared phenytoin versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures. We are uncertain as to the effect of phenytoin versus lorazepam on achieving seizure control after the first loading dose (RR 0.77, 95% CI 0.60 to 0.99; 71 participants; very low-certainty evidence); mortality before hospital discharge (RR 0.44, 95% CI 0.12 to 1.57; 71 participants; very low-certainty evidence); and sedation or drowsiness (RR 0.21, 95% CI 0.01 to 4.13; 71 participants; very low-certainty evidence). We did not find any data on the impact of phenytoin versus lorazepam as first-line ASM for clinically diagnosed seizures on seizure control after the maximal loading dose of ASM, risk of various adverse effects due to ASM, proportion of infants who develop epilepsy post-discharge and on important long-term outcomes such as mortality or neurodevelopmental disability at 18 to 24 months or cognitive impairment at two years or more.

One trial (Soul 2021) compared phenobarbital + bumetanide versus phenobarbital alone in EEG-confirmed neonatal seizures. Phenobarbital + bumetanide when compared to phenobarbital alone may have little or no effect on seizure control after the first loading dose (RR 0.95, 95% CI 0.37 to 2.40; 43 participants; low-certainty evidence). We are uncertain as to the effect of phenobarbital + bumetanide versus phenobarbital alone on mortality before hospital discharge (RR 0.20, 95% CI 0.02 to 1.74; 43 participants; very low-certainty evidence); cognitive impairment at 18 to 24 months (RR 0.53, 95% CI 0.13 to 2.15; 43 participants; very low-certainty evidence); and proportion of infants who develop epilepsy post-discharge (RR 1.13, 95% CI 0.43 to 2.97; 43 participants; very low-certainty evidence). We did not find any data on the effect of phenobarbital + bumetanide versus phenobarbital alone for EEG-confirmed seizures on seizure control after the maximal loading dose of ASM, risk of various adverse effects due to ASM, and important long-term outcomes such as mortality or neurodevelopmental disability at 18 to 24 months.

One trial (Boylan 2004) compared lignocaine versus benzodiazepines as second-line ASM in clinically diagnosed neonatal seizures. We are uncertain about the effect of lignocaine versus benzodiazepines in achieving seizure control after the maximal loading dose (RR 8.17, 95% CI 0.52 to 128.42; 11 participants; very low-certainty evidence); mortality or neurodevelopmental disability at 12 months (RR 1.00, 95% CI 0.71 to 1.41; 10 participants; very low-certainty evidence); all-cause mortality before hospital discharge (RR 1.20, 95% CI 0.25 to 5.71; 11 participants; very low-certainty evidence); and neurodevelopmental disability at 12 months (RR 1.00, 95% CI 0.36 to 2.75; 10 participants; very low-certainty evidence). We did not find any data on the effect of lignocaine versus benzodiazepines as second-line ASM on seizure control after the first loading dose of ASM, risk of various adverse effects due to ASM, and proportion of infants who develop epilepsy post-discharge.

Two trials (Srinivasakumar 2015; Van Rooji 2010) compared the treatment of both clinical and electrographic seizures versus treating clinical seizures alone in neonates. Treatment of clinical and electrographic seizures when compared to treating clinical seizures alone may have little or no effect on seizure burden during hospitalisation (MD -1871.16, 95% CI -4525.05 to 782.73; 68 participants; low-certainty evidence); mortality before hospital discharge (RR 0.59, 95% CI 0.28 to 1.27; 68 participants; low-certainty evidence); and proportion of infants who develop epilepsy post-discharge (RR 0.75, 95% CI 0.12 to 4.73; 35 participants; low-certainty evidence). We found no data on the effect of treating clinical and electrographic seizures compared to treating clinical seizures alone on adverse effects due to ASM and other important long-term outcomes such as mortality or neurodevelopmental disability at 18 to 24 months or cognitive impairment at two years or more.

Two trials (Jindal 2021; Saxena 2016) compared maintenance therapy with ASM versus no maintenance therapy after achieving seizure control in neonatal seizures. We are uncertain about the effect of maintenance therapy with ASM versus no maintenance therapy on the recurrence of seizures before hospital discharge (RR 0.76, 95% CI 0.56 to 1.01; 373 participants; very low-certainty evidence). Maintenance therapy with ASM compared to no maintenance therapy may have little or no effect on mortality before hospital discharge (RR 0.69, 95% CI 0.39 to 1.22; 373 participants; low-certainty evidence); mortality by 18 to 24 months (RR 0.94, 95% CI 0.34 to 2.61; 111 participants; low-certainty evidence); neurodevelopmental disability by 18 to 24 months (RR 0.89, 95% CI 0.13 to 6.12; 108 participants; low-certainty evidence);- and proportion of infants with epilepsy post discharge (RR 3.18, 95% CI 0.69 to 14.72; 126 participants; low-certainty evidence).

Overall completeness and applicability of evidence

Phenobarbital is probably more effective than levetiracetam as first-line ASM in achieving seizure control in neonates with EEG-confirmed seizures after both the first loading dose and the maximal loading dose of ASM (moderate-certainty evidence). Phenobarbital may be more effective than phenytoin as first-line ASM in achieving seizure control in clinically diagnosed seizures after the first loading dose of ASM (low-certainty evidence). Phenobarbital + bumetanide may have little or no difference in achieving seizure control when compared to phenobarbital alone in EEG-confirmed seizures (low-certainty evidence). These results apply to term and late preterm neonates who have seizures due to any aetiology other than hypoglycaemia and hypocalcaemia. None of the included studies had recruited preterm neonates born at < 34 weeks' gestational age. Hence, the results cannot be used for this preterm population. For other comparisons of one ASM

versus another to achieve seizure control, limited data and very low-certainty evidence preclude us from drawing any reasonable conclusions.

We are uncertain as to the effect of one ASM versus another on other short-term outcomes including mortality before hospital discharge. Most of the trials have included neonates who required other ASMs as well for seizure control. Hence, all the short- and long-term outcomes other than seizure control would have been influenced by other ASMs as well. We did not analyse monotherapy and polytherapy separately due to the non-availability of adequate data. Most trials did not provide data on long-term outcomes such as mortality, neurodevelopmental disability or cognitive impairment. As the long-term neurodevelopmental outcomes are the major determinant for the choice of ASM, the lack of data on long-term outcomes is a major drawback in interpreting the results of this review.

It is well recognised that detection of neonatal seizures on a clinical observation basis alone is unreliable because most infants have only subtle clinical manifestations which are often missed in a clinical setting. In addition, clinical diagnosis has poor diagnostic accuracy as clinical behaviours are often misinterpreted as seizures (Murray 2008). In fact, one study revealed that even experts only correctly diagnosed 50% of events if relying on clinical observation only (Malone 2009). It is also known that many seizures are electrographic-only or subclinical, particularly after treatment with some types of ASM which are known to induce uncoupling (Boylan 2002;Hahn 2004; Scher 2003). Electrographic seizures are also the most common seizure type in critical neonates as they are often on sedation, pain relief or muscle relaxation. In order for clinical trials to be meaningful and transferable, it is essential that outcome measures are well-defined and can be measured accurately and precisely (Heneghan 2017). For the reasons outlined above, clinical diagnosis of seizures is neither. Thus, trials using clinical diagnosis should not be used for licencing ASM or to inform clinical guidelines or recommendations. Hence, the conclusions of this review are based on trials that used EEG-confirmed seizures.

Treatment of both clinical and electrographic seizures, when compared with treating clinical seizures alone, may have little or no effect on mortality before hospital discharge, seizure burden during hospitalisation, and the proportion of infants who develop epilepsy post-discharge (low-certainty evidence). Since both the trials included only neonates with HIE, the results are applicable only to this subgroup. There were no data on long-term mortality or neurodevelopmental outcomes.

Short-term maintenance therapy with ASM after achieving seizure control when compared to no maintenance ASM may have little or no effect on mortality before hospital discharge, mortality by 18 to 24 months, neurodevelopmental disability by 18 to 24 months, and the proportion of infants with epilepsy post-discharge (low-certainty evidence). Both trials included only those neonates who achieved seizure control after the first loading dose of phenobarbital. Hence, the results do not apply to neonates who require more than one ASM for seizure control.

Quality of the evidence

For the comparison, phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures, the certainty of evidence was moderate for the outcomes: seizure control after first loading dose of ASM and seizure control after maximal loading dose of ASM (downgraded by one level for serious imprecision due to the small size not meeting the 'Optimal Information Size' criteria); and the certainty of evidence was very low for the outcomes: mortality before hospital discharge, requirement of mechanical ventilation, sedation or drowsiness, and proportion of infants with epilepsy post-discharge (downgraded by one level for indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well and by two levels for very serious imprecision due to a wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria).

For the comparison, phenobarbital versus levetiracetam as first-line ASM for clinically diagnosed neonatal seizures, the certainty of evidence was very low for the outcomes: seizure control after first loading dose of ASM (downgraded by two levels for very serious risk of bias due to 'high risk of bias' in two trials and some concerns in the other trial and by one level for serious imprecision due to small sample size not meeting the 'Optimal Information Size' criterion); seizure control after maximal loading dose of ASM (downgraded by two levels for very serious risk of bias due to high risk of bias in all the three included trials and by one level for serious imprecision due to small sample size not meeting the 'Optimal Information Size' criterion); requirement of mechanical ventilation (downgraded by two levels for very serious imprecision due to a single digit event rate and by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well); sedation or drowsiness (downgraded by two levels for very serious risk of bias due to high risk of bias in all included trials, and by one level for serious inconsistency, serious imprecision and serious indirectness); and proportion of infants with epilepsy post-discharge (downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial and for very serious imprecision). The certainty of evidence was low for mortality before hospital discharge (downgraded by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well and by one level for serious imprecision due to a low event rate not meeting the 'Optimal Information Size' criteria).

For the comparison, phenobarbital versus phenytoin as first-line ASM for EEG-confirmed neonatal seizures, the certainty of evidence was very low for the outcome: seizure control after maximal loading dose of ASM (downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial and by two levels for very serious imprecision due to a wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria).

For the comparison, phenobarbital versus phenytoin as first-line ASM for clinically diagnosed neonatal seizures, the certainty of evidence was low for the outcome: seizure control after the first loading dose of ASM (downgraded by one level for serious risk of bias as the trial contributing > 50% weighting to the estimate has a high risk of overall bias and by one level for serious inconsistency as there was considerable heterogeneity (I^2 = 96%)). The certainty of evidence was very low for mortality before hospital discharge (downgraded by one level for serious inconsistency as there was substantial heterogeneity (I^2 = 82%); by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well; and

by one level for serious imprecision for sample size and event rate not meeting the 'Optimal Information Size' criteria); requirement for mechanical ventilation (downgraded by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well; and by two levels for very serious imprecision due to wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria); sedation or drowsiness (downgraded by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well; by two levels for very serious imprecision due to wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria; and by two levels for very serious risk of bias due to high risk of bias in the only included trial).

For the comparison, phenobarbital versus lorazepam as first-line ASM for clinically diagnosed neonatal seizures, the certainty of evidence was very low for all the outcomes: seizure control after the first loading dose of ASM (downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial and by one level for serious imprecision for sample size and event rate not meeting the 'Optimal Information Size' criteria); mortality before hospital discharge; and sedation or drowsiness (downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial, by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs, as well and by two levels for very serious imprecision due to wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria).

For the comparison, phenytoin versus lorazepam as first-line ASM for clinically diagnosed neonatal seizures, the certainty of evidence was very low for all the outcomes: seizure control after the first loading dose of ASM (downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial and by one level for serious imprecision for sample size and event rate not meeting the 'Optimal Information Size' criteria); mortality before hospital discharge; and sedation or drowsiness (downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial, by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs as well and by two levels for very serious imprecision due to a wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria).

For the comparison, phenobarbital + bumetanide versus phenobarbital alone for EEG-confirmed neonatal seizures, the certainty of evidence was low for the outcome: seizure control after the first loading dose of ASM (downgraded by two levels for very serious imprecision due to a wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria); and very low for the outcomes: mortality before hospital discharge, cognitive impairment at 18 to 24 months and proportion of infants with epilepsy post-discharge (downgraded by two levels for very serious imprecision due to a wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria, and by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs, as well).

For the comparison, lignocaine versus benzodiazepines as second-line ASM for EEG-confirmed neonatal seizures, the certainty of evidence was very low for all the outcomes: seizure control after maximal loading dose of ASM (downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial and by two levels for very serious imprecision due to a wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria); mortality or neurodevelopmental disability at 12 months; all-cause mortality before hospital discharge; and neurodevelopmental disability at 12 months (downgraded by two levels for very serious risk of bias due to high risk of bias in the only included trial and by two levels for very serious imprecision due to a wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria, and by one level for serious indirectness of the intervention as the study population included neonates who required second- and third-line ASMs, as well).

For the comparison, treating both clinical and electrographic seizures versus clinical seizures alone, the certainty of evidence was low for all the outcomes: mortality before hospital discharge, seizure burden during hospitalisation, and proportion of infants with epilepsy post-discharge (downgraded by two levels for very serious imprecision due to a wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria).

For the comparison, maintenance therapy with ASM after achieving seizure control versus no maintenance ASM, the certainty of evidence was very low for repeat seizures before hospital discharge (downgraded by one level for risk of bias due to some concerns in the risk of bias in both the included studies, and by two levels for very serious imprecision due to a wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria); and low for other outcomes: mortality before hospital discharge, mortality at 18 to 24 months, neurodevelopmental disability at 18 to 24 months and proportion of infants who develop epilepsy post-discharge (downgraded by two levels for very serious imprecision due to a wide confidence interval crossing the line of no difference, and sample size and event rate not meeting the 'Optimal Information Size' criteria).

Potential biases in the review process

We performed a comprehensive search of the medical literature to identify all RCTs evaluating the role of ASMs for neonates with seizures. However, although it is unlikely that we missed large relevant studies, it is still possible that we failed to identify small studies whose results have been published in abstract proceedings or in less accessible literature. We made every effort to contact the authors of any included study asking them to provide missing data. Furthermore, some authors of the present review were inevitably already familiar with most of the included studies.

Agreements and disagreements with other studies or reviews

Other systematic reviews have previously addressed the topic of treatment of neonatal seizures. Only the previous Cochrane Review (Booth 2004), and the International League Against Epilepsy/World Health Organization (ILAE/WHO) guidelines (WHO 2011) adopted a similar comprehensive approach as our review. Both these previous reviews included only studies on EEG-confirmed seizures. They concluded that phenobarbital is the recommended ASM in neonates, but the certainty of evidence was very low. Such a discrepancy in certainty of evidence is due to the inclusion of the recently published NEOLEV2 study (Sharpe 2020) in our review. Other systematic reviews were limited to a literature search and, although they limited their search to EEG-confirmed seizures, they did not synthesise results with meta-analysis (Falsaperla 2021; Hellström-Westas 2015; Slaughter 2013). One other systematic review used a different approach (network meta-analysis) and thus is not easily comparable with ours (Xu 2021). Most of the other reviews evaluated single ASMs such as levetiracetam (Hooper 2021; McHugh 2018; Sharma 2022), phenobarbital (Kumar 2021), or levetiracetam versus phenobarbital (Qiao 2021), or they limited the review to a single aetiology such as stroke (Sortino 2022), and inborn errors of metabolism (Falsaperla 2021). All of these included only or mostly retrospective and uncontrolled studies. Thus, their evidence is of very low certainty and no strong recommendations can be based on this.

The present systematic review is the first to evaluate evidence on the duration of treatment. The ILAE/WHO guidelines (WHO 2011) recommended stopping ASM before discharge, but this was an expert opinion not based on data from the literature.

AUTHORS' CONCLUSIONS

Implications for practice

Phenobarbital is probably more effective than levetiracetam in achieving seizure control after the first loading dose and after the maximal loading dose (moderate-certainty evidence). Phenobarbital may be more effective than phenytoin in achieving seizure control after the first loading dose (low-certainty evidence). However, as the latter finding is based on trials that utilised clinical diagnosis of seizures, this needs to be confirmed by a well-powered RCT evaluating EEG-confirmed seizures. Phenobarbital + bumetanide may have little or no difference in achieving seizure control when compared to phenobarbital alone (low-certainty evidence). Limited data and very low-certainty evidence preclude us from drawing any reasonable conclusion on the effect of using one ASM versus another on other short- and long-term outcomes.

In neonates with HIE, treatment of both clinical and electrographic seizures when compared to treating clinical seizures alone may have little or no effect on mortality before hospital discharge, seizure burden during hospitalisation, and the proportion of infants who develop epilepsy post-discharge (low-certainty evidence).

In neonates who achieve seizure control after the first loading dose of phenobarbital, maintenance therapy with ASM when compared to no maintenance ASM may have little or no effect on mortality before hospital discharge, mortality by 18 to 24 months, neurodevelopmental disability by 18 to 24 months, and proportion of infants with epilepsy post-discharge (low-certainty evidence).

All findings of this review apply only to term and late preterm neonates.

We identified 23 studies that were registered as ongoing. However, most of these were either entered into the registry five to 10 years ago without follow-up, or results were not published in spite of the apparently achieved sample size. We identified one study investigating treatment duration that may change the conclusions of this review (NCT04320940).

Implications for research

We need well-designed RCTs evaluating the effect of one ASM versus another to improve the precision of the results. These RCTs should use EEG to diagnose seizures, as clinical diagnosis of seizures is prone to errors and inaccurate. These studies should be adequately powered to assess the effect of ASMs on long-term neurodevelopmental outcomes. As seizures are not uncommon in preterm neonates, we need separate RCTs evaluating the choice of ASM in this vulnerable population.

Similarly, the other two questions 'whether to treat only-electrographic seizures with ASM or not' and 'whether to give routine maintenance therapy with ASM after achieving seizure control with loading doses of ASM' are very pertinent for the clinical management of neonates with seizures. We need further RCTs on these to evaluate the effect of ASM on short- and long-term outcomes with more precision.

ACKNOWLEDGEMENTS

The Methods section of this review is based on a standard template used by Cochrane Neonatal.

We would like to thank Cochrane Neonatal: Michelle Fiander and Jane Cracknell, Managing Editors; and Roger Soll and Bill McGuire, Co-coordinating Editors, who provided editorial and administrative support. Michelle Fiander (Information Specialist), who designed the literature searches and search methods; and Chris Cooper (Information Specialist) who ran the searches.

We would like to thank the authors Raffaele Falsaperla, Tafazzal Hossain Khan, Ankush Jindal, Cynthia Sharpe and Janet Soul for providing additional data and details regarding their trials.

We thank the following peer reviewers:

Dr. Manigandan Chandrasekaran MD FRCPCH, Consultant Neonatologist, Liverpool Women's Hospital NHS Foundation Trust.

Balamurugan Palanisami, Liverpool Women's Hospital NHS Foundation Trust, UK.

We would also like to thank Anne Lethaby, Cochrane Central Production Service, for copy editing the review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Akeel 2022

Study characteristics	
Methods	Prospective double-blind randomised controlled trial
Participants	Neonates with seizures, diagnosis based on clinical examination. Both full-term neonates as well as preterm included. Exclusion criteria: acute electrolyte disturbance, inborn error of metabolism, opioid withdrawal syndrome, ASM given prior to inclusion 136 neonates screened, 104 included The study was performed in a tertiary care centre in Benha, Egypt, between March 2020 and March 2022.
Interventions	Group A: Phenobarbital IV or orally, loading dose 20 mg/kg, second loading if not successful with 10 mg/kg. If successful, PB continued as maintenance (5 mg/kg*d). Add-on of LEV if not successful after 40 min. Group B: Levetiracetam IV or orally, loading dose 20 mg/kg, second loading if not successful with 10 mg/kg. If successful, LEV continued as maintenance (20 mg/kg*d). Add-on of PB if not successful after 40 min.

Akeel 2022 *(Continued)*

Outcomes	Primary outcome: clinical cessation of seizures within 20/40 min of IV drug application and seizure-free for the following 24 hrs. Secondary outcome: adverse events
Notes	Demographic data and seizure aetiology show some differences between both groups (gestational diabetes mellitus, maternal hypertension, perinatal asphyxia). Seizure control (clinical impression) was better in the LEV group than in the PB group. Adverse events were more frequent in the PB group, including need for mechanical ventilation in 2/52. No information is given on EEG findings in participants. The authors reported no conflicting interests and no external funding for the research.

Boylan 2004

Study characteristics	
Methods	Randomised controlled trial
Participants	Neonates with seizures who failed to respond to first-line phenobarbitone treatment (Quote:) "Neonates at high risk of developing seizures because of birth depression or cord blood acidosis, had abnormal movements suggesting seizures, or had meningitis. Neonates who had already received a single loading dose of phenobarbitone were not excluded from the study." Sample size was 27 neonates with EEG-confirmed seizures, 5 were excluded because of protocol violations, 11 because they responded to phenobarbitone. 11 neonates were included in the analysis because they required second-line treatments (3 clonazepam, 5 lignocaine, 3 midazolam). The study was performed in 2 neonatal intensive care units in London, UK. Information on study dates is not included in the publication.
Interventions	First-line treatment (in all neonates, before randomisation): phenobarbitone in a dose of up to 40 mg/kg. (Quote:) "If this failed to abolish seizures or reduce the seizure burden by at least 80% within 12 hours of enrollment, the neonate was randomly assigned to receive midazolam or lignocaine as second-line anticonvulsant therapy." Second-line treatments: - Midazolam bolus dose of 60 µg/kg followed by an infusion of 150 µg/kg/h, increased to either 300 µg/kg/h if midazolam failed to abolish or reduce seizure burden by at least 80% within 12 hours; - Lignocaine bolus of 4 mg/kg over 20 minutes followed by an infusion of 2 mg/kg/h, increased to 4 mg/kg/h if midazolam failed to abolish or reduce seizure burden by at least 80% within 12 hours; Clonazepam was administered (quote:) "if the increased dose of either drug failed to improve the seizure burden within 48 hours of enrollment" or (quote:)"if parents were not willing for their child to be given a drug chosen randomly".
Outcomes	Primary endpoint: control of electrographic seizures, defined as (quote:) "complete absence of seizure activity on the EEG or a reduction of > 80% of pretreatment burden" Other endpoints: neurodevelopmental assessment evaluated with Amiel–Tison and Griffiths neurodevelopmental assessment at 1 year.
Notes	Response to treatment was assessed using continuous video-EEG.

Boylan 2004 *(Continued)*

	(Quote:) "All neonates were monitored continuously for at least 24 hours after enrollment. If electrographic seizures were not detected during this time, recording was stopped. If seizures were present, monitoring was continued until seizure control was established or treatment was considered to have failed (at least 48 hours later)." Neonates receiving lignocaine continued to be given background midazolam at a dose of 30 to 60 µg/kg/h. Some neonates were also receiving continuous low-dose morphine as analgesia (10 to 20 µg/kg/h). External funding sources or possible conflicts of interests were not mentioned in the publication.

Falsaperla 2019

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (quote)"term neonates with seizures manifesting within the first 28 days of life." Exclusion criteria: (quote:)"Newborns with SE, GE, and seizures secondary to transient metabolic disorders, including hypoglycaemia and hypocalcaemia; neonates with a positive history for maternal drug ingestion; those who received more than one anticonvulsant medication; and those neonates in whom LEV was used as second-line therapy" The study was performed at a single centre in Catania, Italy. Patients were recruited between February 2016 and February 2018. **LEV group** Number of patients: 15 Gestational age: 38.13 ± 1.24 Sex (F/M): 4/11 Prenatal anomalies: 40% APGAR score 1 min: 7 66 ± 1.29 APGAR score 5 min: 9 13 ± 1.12 Respiratory distress: 33.33% ***PB group*** Number of patients: 15 Gestational age: 38.33 ± 1.04 Sex (F/M): 8/7 Prenatal anomalies: 40% APGAR score 1 min: 8 66 ± 0 89 APGAR score 5 min: 9.03 ± 0.84 Respiratory distress: 40%
Interventions	Intravenous PB, initial dose of 20 mg/kg, followed by a maintenance dose of oral PB at 5 mg/kg; Intravenous LEV, initial dose of 20 mg/kg, followed by a maintenance dose of oral LEV at 20 mg/kg, with gradually increasing doses up to 40 mg/kg twice daily in case of nonresponse at initial doses. Therapy was maintained for one month after the seizures resolved.
Outcomes	Neurodevelopmental outcomes evaluated with HNNE at baseline and after 1 month of treatment. The assessment was made by trained neonatologists, who evaluated the following neurological items: (1) tone and posture, (2) tone patterns, (3) movements, (4) reflexes, (5) abnormal signs, and (6) orientation and behaviour.

Falsaperla 2019 *(Continued)*

Notes	External funding sources were not mentioned. All authors reported not having potential conflicts of interest to disclose.

Ghaffar 2020

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (quote:) "1. Age < 28 days; 2. Both genders; 3. Neonatal seizures as per operational definition for < 24 hours" Exclusion criteria: (quote:) "1. Who were already receiving anticonvulsants; 2. If seizures were due to correctable metabolic abnormalities (i.e. hypoglycaemia, hypocalcaemia, hypomagnesaemia, hyponatraemia); 3. Neonates with associated pulmonary, hepatic, renal, or cardiac dysfunction." **PB group** Number of patients: 30 Age (days, mean ± SD): 15.20 ± 5.62 14.90 ± 5.99 Male: 19 (63.3%) Duration of complaint (hours): 10.40 ± 4.83 Weight (kg): 4.056 ± 0.65 **LEV group** Number of patients: 30 Age (days, mean ± SD): 14.90 ± 5.99 Male: 19 (63.3%) Duration of complaint (hours): 11.433 ± 4.67 Weight (kg): 4.163 ± 0.64 The study was conducted at a single centre in Sialcot, Pakistan, from January 2019 to February 2020.
Interventions	**PB group:** (Quote:) "Intravenous loading dose maximum 40 mg/kg (initial loading dose 20 mg/kg reloading with 10 mg/kg for further 2 times) and maintenance dose 5 mg/kg." Given in infusion form in dilution in 15 mL normal saline over 15 minutes. **LEV group:** (Quote:) "Intravenous loading maximum 40 mg/kg (initially with 30 mg/kg then reloading with 10 mg/kg) and maintenance dose 20 mg/kg/day." Given in infusion form in dilution in 15 mL normal saline over 15 minutes. If seizures reoccur with maximum loading dose, then the patient was switched to other drug. Patient was continuously monitored and observed for reoccurrence of seizures within 24 hours.

Ghaffar 2020 *(Continued)*

Outcomes	(Quote:)"Efficacy as per operational definition was noted after 24 hours by the researcher himself." No further details were provided.
Notes	External funding sources were not mentioned in the publication. The authors reported not having potential conflicts of interest to disclose.

Gowda 2019

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (Quote:) "Outborn neonates (age 0-28 days) with clinical seizures". (Quote:) "Neonatal seizures were clinically defined as abnormal, stereotyped and paroxysmal dysfunction in the CNS, occurring within the first 28 days after birth in full-term infants or before 48 weeks of gestational age in preterm infants." Exclusion criteria: (Quote:) "Neonates with hypoglycaemia, hypocalcaemia, hypomagnesaemia, those who received anticonvulsants prior to enrolment, and those with major congenital malformations e.g. congenital heart defects, neural tube malformations, diaphragmatic hernia, choanal atresia, oesophageal atresia, tracheo-oesophageal fistula, omphalocele, gastroschisis, intestinal obstruction and imperforate anus". **LEV group, 50 patients** Age (days), mean (SD): 9.8 (8.50) Male, n (%): 28 (56) *Mode of delivery, n (%)* Vaginal: 35 (70) Caesarian: 15 (30) *Gestation, n (%)* Term: 40 (80), 42 (84) Preterm: 10 (20), 08 (16) Birth weight (kg), mean (SD): 2.56 (0.64) *Aetiology of seizures, n (%)* Hypoxic ischaemic encephalopathy: 20 (40) Neonatal sepsis/meningitis: 18 (36) Intracranial haemorrhage: 3 (6) Benign neonatal epilepsy syndrome: 2 (4) Malignant neonatal epilepsy syndrome: 1 (2) Cortical malformation: 1 (2) Inborn errors of metabolism: 1 (2) Unknown: 4 (8) **PB group, 50 patients** Age (days), mean (SD): 8 (8.33) Male, n (%): 28 (56) *Mode of delivery, n (%)* Vaginal: 36 (72) Caesarian: 14 (28) *Gestation, n (%)* Term: 42 (84) Preterm: 08 (16) Birth weight (kg), mean (SD): 2.73 (0.64) *Aetiology of seizures, n (%)* Hypoxic ischaemic encephalopathy: 24 (48) Neonatal sepsis/meningitis: 15 (30)

Gowda 2019 *(Continued)*

	Intracranial haemorrhage: 2 (4) Benign neonatal epilepsy syndrome: 1 (2) Malignant neonatal epilepsy syndrome: 1 (2) Cortical malformation: 1 (2) Inborn errors of metabolism: 2 (4) Unknown: 4 (8) The study was performed at a single neonatal intensive care unit in Bangalore, India, between November 2014 and April 2016.
Interventions	Intravenous LEV (20 mg/kg) at a rate of 1 mg/kg/min under cardiorespiratory monitoring. If seizures terminated, LEV was continued as maintenance at 20 mg/kg/day in 2 divided doses. If seizures continued, another loading dose of LEV (20 mg/kg) was injected, and if seizures still persisted, patient was switched over to PB. Intravenous PB (20 mg/kg) administered in the dose of 20 mg/kg diluted in 1:10 normal saline given intravenously slowly at the rate of 1 mg/kg/min under cardiorespiratory monitoring; if seizures were terminated, it was continued at 5 mg/kg/day in 2 divided doses as maintenance. Another loading dose of 10 mg/kg of PB was administered in neonates who failed to respond, and if seizures still persisted after 2 loading doses, patient was switched over to LEV.
Outcomes	Primary outcomes: (quote:) "proportion of patients achieving cessation of seizures following the first or second dose of the drug (PB or LEV), and those remaining seizure-free for next 24 hours". (Quote:)"Termination of seizures was defined clinically if there were no abnormal movement/eyeball deviation/nystagmus, no change in heart rate, no change in respiration/saturation and autonomic dysfunction". Secondary outcomes: proportion of patients experiencing (quote:)"adverse events occurring within two hours of drug administration, including desaturation, reduced respiratory rate, increased ventilator support requirement, arrhythmias, blood pressure, or heart rate fluctuations by more than 10% compared to the previous 2 hours, or if vasopressors were initiated or increased".
Notes	The authors stated there was no external funding. The authors reported not having potential conflicts of interest to disclose.

Jindal 2021

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: neonates 34 weeks of gestation to < 28 days of postnatal period admitted with neonatal seizure Exclusion criteria: neonates on 2 antiseizure medication; HIE stage III; metabolic cause (hypocalcaemia, hypoglycaemia); intracranial bleeding, brain infarct; major congenital malformation suspected storage disorders, IEM, chromosomal anomalies, and IUI; seizure recurrence within 12 hours of phenobarbitone loading; < 34 weeks of gestation; and > 28 days of postnatal life The study was performed in a single neonatal unit at a tertiary care hospital in India between January 2019 and December 2019.
Interventions	After a loading dose of PB (20 mg/kg), neonates who remained seizure-free for at least 12 hours were enrolled. Group A: PB withdrawal group: (quote:)"phenobarbitone maintenance was stopped" (no further details reported)

Jindal 2021 *(Continued)*

Group B: PB continued group: (quote:)"PB maintenance was continued until discharge and further continuation was decided based on clinician's discretion." (no further details reported)

PB withdrawal group (n = 112)

Male, n (%): 73 (65.2)

Age (days), mean (SD): 6.5 (1.8)

Gestation (weeks), mean (SD): 37.1 (2.5)

Birth weight (grams), mean (SD): 2536 (560)

Antenatal comorbidities

PIH, *n* (%): 3 (2.7)

PROM, *n* (%): 13 (11.6)

Foetal distress, *n* (%): 25 (22.3)

Mode of delivery

NVD, *n* (%): 75 (67)

LSCS, *n* (%): 36 (32.1)

Instrumentation, *n* (%): 1 (0.9)

Resuscitation details

Delayed cry at birth, *n* (%): 55 (49.1)

Needed resuscitation, *n* (%): 53 (47.3)

Postnatal neurological abnormality, *n* (%): 50 (44.6)

Weight for age

AGA, *n* (%): 69 (61.6)

SGA, *n* (%): 42 (37.5)

LGA, *n* (%): 1 (0.9)

Anthropometry at admission

Weight (grams), mean (SD): 2529 (566)

Length (cm), mean (SD): 49.1 (2.9)

Head circumference (cm), mean (SD): 31.5 (1.7)

Abnormal neurological examination, *n* (%): 71 (63.4)

Bulging anterior fontanelle, *n* (%): 4 (3.6)

Tone

Increased, n (%): 6 (5.4)

Decreased, n (%): 48 (42.9)

Abnormal posture, *n* (%): 36 (32.1)

Deep tendon reflexes

Exaggerated, *n (%):* 4 (3.6)

Jindal 2021 *(Continued)*

Absent, n (%): 51 (45.5)

Abnormal primitive neonatal reflexes, *n* (%): 64 (57.1)

Abnormal pupillary reactions, *n* (%): 19 (17.0)

Abnormal respiratory system, *n* (%): 24 (21.4)

Abnormal cardiovascular system, *n* (%): 3 (2.7)

Abnormal abdomen examination, *n* (%): 5 (4.5)

Seizure onset (day of life), mean (SD): 4.0 (1.4)

Frequency of seizures (episodes/day), mean (SD): 2.9 (1.6)

Seizure semiology

Subtle, *n* (%): 23 (20.5)

Focal tonic, *n* (%): 26 (23.2)

Focal clonic, *n* (%): 26 (23.2)

Generalised tonic, *n* (%): 35 (31.2)

Myoclonic, *n* (%): 2 (1.8)

Autonomic changes, *n* (%): 9 (8)

Status epilepticus, *n* (%): 11 (9.8)

Phenobarbitone continued group (n = 109)

Male, *n* (%): 75 (68.8)

Age (days), mean (SD): 7.8 (2.1)

Gestation (weeks), mean (SD): 37.1 (2.8)

Birth weight (grams), mean (SD): 2527 (568)

Antenatal comorbidities

PIH, *n* (%): 10 (9.2)

PROM, *n* (%): 9 (7.3)

Foetal distress, *n* (%): 19 (17.4)

Mode of delivery

NVD, *n* (%): 81 (74.3)

LSCS, *n* (%): 28 (25.7)

Instrumentation, *n* (%): 0 (0)

Resuscitation details

Delayed cry at birth, *n* (%): 44 (40.4)

Needed resuscitation, *n* (%): 43 (39.4)

Postnatal neurological abnormality, *n* (%): 39 (35.8)

Weight for age

Jindal 2021 *(Continued)*

	AGA, *n* (%): 71 (65.1) SGA, *n* (%): 37 (33.9) LGA, *n* (%): 1 (0.9) ***Anthropometry at admission*** Weight (grams), mean (SD): 2502 (568) Length (cm), mean (SD): 49.0 (2.9) Head circumference (cm), mean (SD): 31.4 (1.6) Abnormal neurological examination, *n* (%): 69 (63.3) ***Tone*** Increased, *n* (%): 11 (10.1) Decreased, *n* (%): 42 (38.5) Abnormal posture, *n* (%): 33 (30.3) *Deep tendon reflexes* Exaggerated, *n* (%): 4 (3.7) Absent, *n* (%): 46 (42.2) Abnormal primitive neonatal reflexes, *n* (%): 62 (56.9) Abnormal pupillary reactions, *n* (%): 15 (13.8) Abnormal respiratory system, *n* (%): 22 (20.2) Abnormal cardiovascular system, *n* (%): 4 (3.7) Abnormal abdomen examination, *n* (%): 2 (1.8) Seizure onset (day of life), mean (SD): 5.6 (1.9) Frequency of seizures (episodes/day), mean (SD): 3.1 (1.5) ***Seizure semiology*** Subtle, *n* (%): 16 (14.7) Focal tonic, *n* (%): 15 (13.8) Focal clonic, *n* (%): 35 (32.1) Generalised tonic, *n* (%): 39 (35.8) Myoclonic, *n* (%): 4 (3.7) Autonomic changes, *n* (%): 10 (9.2) Status epilepticus, *n* (%): 13 (11.9)
Outcomes	Primary outcome: seizure recurrence Secondary outcomes: (quote:) "time to reach full enteral feeds, duration of hospital stay, neurological status at discharge, and mortality."
Notes	The diagnosis of seizure was made on the basis of history and clinical observation and all types of clinical seizures were included.

Jindal 2021 *(Continued)*

	The authors declared there was no external funding. The authors declared they had no competing financial interests or personal relationships that could have appeared to influence the work.

Khan 2020

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (quote:) "premature newborns with a gestational age more than 34 weeks to less than 42 weeks and a birth weight of more than 2000 gm with neonatal seizures" Exclusion criteria: (quote:) "seizures caused by hypoglycaemia, hypocalcaemia or dyselectrolytaemia and sepsis." (Quote:) "Patients [who] had already received more than single loading doses of PB or medication with any other ASMs." ***LEV group, 50 patients*** Sex: male 30 (60.0); female 20 (40.0) *Gestational age (weeks):* Premature (< 37) 6 (12.0); full term (37-42) 44 (88.0) Birth weight (gm): 2000-< 2500 8 (16.0); 2500-4000 42(84.0) *Breathing status of neonates delivered outside hospital (n = 26):* Within 1 minute 19 (79.2); breathing < 5 minutes 5 (20.8) ***PB group, 50 patients*** Sex: male 37 (74.0); female 13 (26.0) *Gestational age (weeks):* Premature (< 37) 5 (10.0); full term (37-42) 45 (90.0) Birth weight (gm): 2000-< 2500 9 (18.0); 2500-4000 41(82.0) *Breathing status of neonates delivered outside hospital (n = 14):* Within 1 minute 31 (86.1); breathing < 5 minutes 5 (13.9) The study was performed at a single centre in Dhaka, Bangladesh. Patients were enrolled between July 2013 and June 2014.
Interventions	Intravenous LEV, loading dose of 50 mg/kg with 10 mg/kg/dose 8-hourly (maintenance) Intravenous PB, loading dose of 20 mg/kg with 5 mg/kg/day 12-hourly (maintenance) If seizures recurred, a second or third loading of PB were given as a dose of 10 mg/kg.
Outcomes	(Quote:) "Control of seizures and time required to control seizures" (Quote:)"Study end point was up to 48 hours but if seizure was not controlled within 48 hours it was labeled as treatment failure."
Notes	(Quote:) "Seizures were diagnosed clinically. No continuous EEG monitoring was performed at time of diagnosis and enrolment." Information on external funding and possible conflicts of interests of the authors was not included in the manuscript.

Painter 1999

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (quote:) "neonates in the neonatal intensive care unit who were at risk for seizures because of reported abnormal movements" and (quote:) "with seizures that were confirmed by electroencephalography"; (quote:)"an Apgar score of less than 5 at five minutes with a base deficit of more than 10 mmol per litre; traumatic delivery; maternal exposure to nonprescription narcotic drugs, amphetamines, or barbiturates; or central nervous system infection or malformation." ***PB group, 30 patients*** *Gestational age (weeks)* ≤ 28: 4 (13) 29–32: 2 (7) 33–37: 5 (17) > 37: 19 (63) Male 14 (47); female 16 (53) *Race* White: 19 (63) Black: 10 (33) Asian: 1 (3) *Primary cause of seizure* Asphyxia, haemorrhage, or infarction: 4 (13) Central nervous system malformations: 2 (7) Central nervous system infection 2 (7) Undetermined 22 (73) ***PHT group, 29 patients*** *Gestational age (wks)* ≤ 28: 1 (3) 29–32: 3 (10) 33–37: 6 (21) > 37: 19 (66) Male 22 (76); female 7 (24) *Race* White: 18 (62) Black: 10 (34) Asian: 1 (3) *Primary cause of seizure* Asphyxia, haemorrhage, or infarction: 27 (93) Central nervous system malformations: 0 (0) Central nervous system infection 1 (3) Undetermined 1 (3) The study was conducted at a single centre in Pittsburgh, USA, between 1990 and 1995.
Interventions	Intravenous phenobarbital administered over a 5 to 15-minute period once daily, with doses needed to achieve plasma concentrations of free drug of 25 µg per millilitre. If the target concentrations had not been achieved, an additional dose was administered, and the assessment process was repeated.

Painter 1999 *(Continued)*

	Intravenous phenytoin administered over a 5 to 15-minute period once daily, with doses needed to achieve plasma concentrations of free drug of 3 µg per millilitre. If the target concentrations had not been achieved, an additional dose was administered, and the assessment process was repeated.
Outcomes	Primary end point: (quote:) "complete control of seizures, as determined by electroencephalographic recording, during treatment with one drug or after the addition of the second drug." (Quote:)"Success", defined as a (quote:) "80 percent reduction in the severity of seizures (calculated as the mean severity per hour) in period 3, or period 5 for neonates receiving both drugs, as compared with the severity in period 1."
Notes	The study was supported by a grant (NS R01 26946-01A2) from the National Institute of Neurological Disorders and Stroke, USA. No information on possible conflicts of interest of the authors was given in the publication.

Pathak 2013

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (quote:) "term or near term neonates (≥ 35 weeks of gestation) admitted with clinically apparent seizures not responding to treatment of hypoglycaemia, hypocalcaemia and other metabolic disorders. Clinical criteria for diagnosis of neonatal seizures were: (i) clonic movement which could be unifocal, multifocal or generalised (ii) tonic posturing with or without abnormal gaze (iii) subtle seizures and spontaneous paroxysmal, repetitive motor or autonomic phenomenon like lip-smacking, chewing, paddling, cyclic movements or respiratory irregularities" Exclusion criteria: (quote:) "Seizures responding to correction of hypoglycaemia, hypocalcaemia or any other metabolic disorder, and babies with major congenital malformation or myoclonic jerks" ***PHT group, 55 patients*** Gestational age (wk), mean (SD): 38.6 (1.45) Weight (kg), mean (SD): 2.71 (0.4) Male sex: 39 (70.9) No of extramural deliveries: 30 (70.9) HIE stage 2: (n = 42) 21 (38.2) HIE stage 3: (n = 44) 26 (47.3) *Cause of seizures* Meningitis: (n = 18) 7 (12.7) Intracranial bleed: (n = 2) 1 (1.8) Kernicterus: (n = 4) 1 (1.8) *Type of seizure* Subtle: 27 (49) Tonic: 24 (43) Clonic: 6 (10.9) ***PB group, 54 patients*** Gestational age (wk), mean (SD): 38.09 (1.87) Weight (kg), mean (SD): 2.55 (0.5) Male sex: 40 (74.1) No of extramural deliveries: 36 (67.0) HIE stage 2: (n = 42) 21 (38.9) HIE stage 3: (n = 44) 18 (33.3) *Cause of seizures*

Pathak 2013 *(Continued)*

	Meningitis: (n = 18) 11 (20.4) Intracranial bleed: (n = 2) 1 (1.9) Kernicterus: (n = 4) 3 (5.6) *Type of seizure* Subtle: 24 (44) Tonic: 20 (37) Clonic: 8 (14) The study was conducted at a level II neonatal unit in Meerut, India from November 2008 to September 2009.
Interventions	Intravenous phenytoin, loading dose of 20 mg/kg administered over 30 minutes at a rate of 1 mg/kg/min. If seizure persisted, the babies were crossed over to intravenous phenobarbitone. Intravenous phenobarbitone, loading dose of 20 mg/kg administered over 30 minutes. If seizure persisted, the babies were crossed over to intravenous phenytoin. (Quote:)"If seizure persisted after two drugs, baby was reloaded with IV phenobarbitone at 10 mg/kg each to a maximum of 40 mg/kg and then a third-line drug like midazolam was used IV at 0.1 mg/kg/dose."
Outcomes	Primary outcome: cessation of clinical seizure activity Secondary outcomes: (quote:) "(i) survival at discharge, (ii) neurodevelopment outcome at 3 months (Amiel-Tieson method), (iii) time taken to control seizures, and (iv) EEG control of seizures."
Notes	According to the authors, there was no external funding. The authors reported not having potential conflicts of interest to disclose.

Perveen 2016

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (quote:) "babies of > 2 kg admitted in NICU within 48 hours of birth with neonatal seizures due to perinatal asphyxia with clinical features of HIE." "If seizures persisted even after correction of hypoglycaemia and hypocalcaemia, babies were randomised for intervention to either levetiracetam or phenobarbitone." Exclusion criteria: anticonvulsant prior to admission; serum creatinine greater than 2 mg/dL; major congenital malformations; refractory shock; need for assisted ventilation at admission. ***LEV group, 30 patients*** Gestational age (weeks), mean (SD): 38.29 (1.03) Weight (kg), mean (SD): 2.78 (0.33) Male: 19 (63.3) Intramural deliveries: 11 (36.7) > 0.05 HIE stage 2: 24 (80) HIE stage 3: 6 (20) Duration of hospital stay, mean (SD): (days) 7.7 (4.56) Need of boluses and inotropic support: 15 (50) Sepsis screen positive: 3/30 (10) ph < 7.0 at admission: 19/30 (63.3) Base deficit > 12: 20/30 (66.6) ***PB group, 30 patients***

Perveen 2016 *(Continued)*

	Gestational age (weeks), mean (SD): 38.43 (1.10) Weight (kg), mean (SD): 2.90 (0.31) Male: 22 (73.3) Intramural deliveries: 13 (43.3) HIE stage 2: 25 (83.3) HIE stage 3: 5 (16.6) Duration of hospital stay (days), mean (SD): 8.9 (4.91) Need of boluses and inotropic support: 10 (30) Sepsis screen positive: 2/30 (6.6) ph < 7.0 at admission: 17/30 (56.6) Base deficit > 12: 18/30 (60) The study was performed at a single centre in Meerut, India, from July 2014 to December 2015.
Interventions	Intravenous LEV, loading dose of 60mg/kg diluted in 30 ml normal saline given slowly over 15 - 20 minutes, under cardio respiratory system monitoring. If seizures were controlled, maintenance was continued (15mg/kg/day every 12 hr) for 5 days. If seizures persisted after the loading dose of LEV, babies crossed over to receive IV phenobarbitone, followed by maintenance (5 mg/kg/day every 12 hr) for 5 days. Intravenous PB, loading dose of 20mg/kg diluted in 1:10 of distilled water given slowly at the rate of 1mg/kg/min under strict cardiorespiratory monitoring. If seizures persisted, the babies were crossed over to treatment with IV levetiracetam. If seizures were controlled then they were kept on maintenance dose of both drugs. If seizures persisted despite crossover, the babies were treated as per unit policy.
Outcomes	Primary outcome: (quote:)"Clinical control of seizure activity ". (Quote:)"Seizures were considered to be controlled if the baby was seizures free 24 hrs after last seizures." Secondary outcomes: (quote:) "safety profile of levetiracetam, electrical seizures after control of clinical seizure, time taken to control seizures, and neurological examination till 6 months."
Notes	According to the others there was no external funding. The authors reported not having potential conflicts of interest to disclose.

Prakash 2019

Study characteristics	
Methods	Randomised controlled trial, not blinded. A block randomisation model (blocks of 4) was used with sealed envelopes. The study was conducted at a tertiary care neonatal intensive care unit at Bihar, India, between April 2018 and September 2019.
Participants	80 newborns with clinically apparent seizures, after acute metabolic disorders were ruled out. Inclusion was based on appearance of motor or autonomic phenomena suggestive of seizures. Exclusion criteria were prematurity, major congenital malformation, intubation at time of admission, newborns presenting with myoclonic jerks. Demographic data at baseline comparable
Interventions	Group A (n = 42) LEV loading 10 mg/kg IV, if seizures persisted additionally 5 mg/kg. Maintenance with dosage that had proved to control seizures. If seizures persisted, 'cross-over' to PB. Group B (n = 38): PB loading 20 mg/kg IV, if seizures persisted, additional 10 mg in aliquots up to a maximum dosage of 40 mg/kg. Maintenance after 24 h. If seizures persisted, 'cross-over' to LEV.

Prakash 2019 *(Continued)*

	Third-line drug midazolam 0.2 mg/kg/dose followed by continuous infusion
Outcomes	Primary outcome variable: cessation of clinical seizure activity for 5 d Secondary outcome variables: time to control seizures, survival at discharge, short-term adverse effects, neurodevelopmental outcome at 12 m, EEG control of seizures
Notes	Cessation of clinical seizures not different between groups. Adverse events (cardiorespiratory depression, sedation) in 3/42 in the LEV group vs 20/38 in the PB group. EEG only after clinical seizures were controlled, not different between groups. Neuromotor developmental delay, 'mental retardation' and comorbidities more frequent in PB group.

Saxena 2016

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (quote:) "term or near-term neonates of ≥ 34 weeks of gestation up to 4 weeks postnatal age and weighing ≥ 2 kg. All types of clinical seizures were included in the study. The diagnosis of seizure was based on clinical observation only." Exclusion criteria: (quote:) "recurrence of seizures within 12 hrs of the loading dose of phenobarbitone, major congenital malformations, suspected storage disease (ruled out by metabolic screen), intrauterine infection (ruled out by serological screen) and suspected chromosomal abnormalities (based on facial dysmorphism and other phenotypic abnormalities)" ***Placebo group, 75 patients*** Weight (g), mean (SD): 2677 (448.7) Gestation (w), mean (SD): 37 (1.3) Male, n (%): 41 (54.7) Intramural delivery, n(%): 28 (37.3) Age at admission (h), median (IQR): 4 (0-28) Onset of convulsion (h), median (IQR): 12 (5-42.5) *HIE (at admission)* Stage I, n (%): 1 (1.3) Stage II 49, n (%): (65.3) Stage III 14, n (%): (18.7) Serum PB level(µg/mL) at 12 hours, mean (SD): 24.8 (23.4) *Aetiology* Birth asphyxia, n (%): 65 (86.7) Meningitis/sepsis, n (%): 6 (8) Metabolic, n (%): 2 (2.7) Intracranial haemorrhage, n (%): 2 (2.7) ***PB group, 77 patients*** Weight (g), mean (SD): 2742 (342.7) Gestation (w), mean (SD): 38 (1.4) Male, n(%): 50 (64.9) Intramural delivery, n (%): 27 (35.0) Age at admission (h), median (IQR): 3 (0-16) Onset of convulsion (h), median (IQR): 12 (4-24) *HIE (at admission)*

Saxena 2016 *(Continued)*

	Stage I, n (%): 4 (5.2) Stage II, n (%): 52 (68.8) Stage III, n (%): 9 (11.7) Serum PB level (µg/mL) at 12 hours, mean (SD): 20.2 (22.0) *Aetiology* Birth asphyxia, n (%): 69 (89.6) Meningitis/sepsis, n (%): 7 (9.1) Metabolic, n (%): 1 (1.3) Intracranial haemorrhage, n (%): 0 The study was conducted at a level II neonatal intensive care unit in India from September 2012 to September 2013.
Interventions	Initial correction of hypoglycaemia and hypocalcaemia, followed by load with intravenous PB at 20 mg/kg in 1:10 dilution with normal saline (NS) over a 15-20-minute period at a rate of 1 mg/kg/min. All responders (subjects who remained seizure-free for a period of 12 hours after loading dose) were randomised into 2 groups. PB (200 mg/mL) was diluted 1:20 in NS (1 mL PB + 19 mL NS) to make its concentration 200 mg/20 mL or 10 mg/ mL. Maintenance dose was 2.5 mg/kg (of PB) which was equivalent to 0.25 mL/kg/dose of prepared solution every 12 hourly for 5 days. Placebo was 20 mL of normal saline kept in an identical syringe. Maintenance dose was equivalent to 0.25 mL/kg/dose of prepared solution every 12 hourly for 5 days. The study intervention stopped after 5 days of seizure-free period. If a breakthrough seizure occurred, the baby was reloaded with 10 mg/kg of PB and put on open-label maintenance of PB till discharge.
Outcomes	Seizure recurrence, mortality, need for inotropic support, time to reach full oral enteral nutrition, duration of hospital stay, neurodevelopment status, seizure recurrence and re-hospitalisation up to 3 months of age.
Notes	The study was partially funded by 'Thesis/-Research grant' of the Indian Council for Medical Research (ICMR). The authors reported not having potential conflicts of interest to disclose.

Sharpe 2020

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: infants at risk of developing seizures or suspected of having seizures. Patients were term infants of a corrected gestational age between 36 and 44 weeks (< 2 weeks of age) with a weight of at least 2.2 kg. Exclusion criteria: (quote) "any previous ASMs (except short-acting benzodiazepines administered for sedation > 24 hours before enrollment), if the serum creatinine level was > 1.6 mg/dL, or if seizures were due to correctable metabolic abnormalities (such as hypoglycaemia or hypocalcaemia). Patients in whom death was imminent were excluded. Patients in whom EEG monitoring could not be commenced before the need to treat definite clinical seizures were not recruited." ***LEV group, 64 patients*** HIE as seizure aetiology, n (%): 35 (55)

Sharpe 2020 *(Continued)*

	Received hypothermia treatment, n (%): 24 (38) Male sex, n (%): 31 (48) Cord pH: n 31; Mean (SD): 7.07 (0.2) 5-min Apgar score, n 64; mean (SD): 6.52 (3.01) Gestational age, n 64; mean (SD): wk 39.3 (1.3) Birth weight n 64; mean (SD): g 3342 (577) Pretreatment seizure severity n 52; mean (SD): min/h 12.3 (12.0) ***PB group, 42 patients*** HIE as seizure aetiology, n (%): 22 (52) Received hypothermia treatment, n (%): 18 (43) Male sex, n (%): 24 (57) Cord pH n 20, mean (SD): 7.15 (0.17) 5-min Apgar score, n 40, mean (SD): 6.47 (2.4) Gestational age, n 42, mean (SD): wk 39.1 (1.3) Birth weight n 42, mean (SD): g 3317 (501) Pretreatment seizure severity, n 29, mean (SD): min/h 9.1 (9.3) The multicentre study was performed at hospitals in San Diego, USA; Oakland, USA, Auckland, New Zealand, and Loma Linda, USA. Patients were enrolled between March 2013 and October 2017.
Interventions	LEV: infusion over 15 minutes at 40 mg/kg, with an additional 15 minutes allowed for the medication to take effect. If electrographic seizures persisted or recurred 15 minutes after the first infusion was complete, an additional dose of the same treatment type was given. Patients who had received LEV at 40 mg/kg received an additional 20 mg/kg infusion over 15 minutes. If electrographic seizures persisted or recurred 15 minutes after the second infusion was complete, the patient was then treated with the alternate treatment. Patients given any LEV loading doses received maintenance LEV at 10 mg/kg per dose, given IV every 8 hours for 5 days. PB: infusion over 15 minutes at 20 mg/kg, with an additional 15 minutes allowed for the medication to take effect. If electrographic seizures persisted or recurred 15 minutes after the first infusion was complete, an additional dose of the same treatment type was given. Patients who had received LEV at 20 mg/kg received an additional 20 mg/kg infusion over 15 minutes. If electrographic seizures persisted or recurred 15 minutes after the second infusion was complete, the patient was then treated with the alternate treatment. Patients given any PB loading doses received maintenance PB at 1.5 mg/kg per dose, given IV every 8 hours for 5 days.
Outcomes	Primary outcome: rate of achieving and maintaining electrographic seizure freedom for 24 hours Secondary outcomes: seizure cessation for 48 hours; rate of achieving and maintaining seizure freedom for 1 hour; subanalyses of the primary outcome measure for subjects with hypoxic-ischaemic encephalopathy (HIE) who underwent therapeutic hypothermia
Notes	Funding: quote: "The NEOLEV2 study was funded by the US Food and Drug Administration Orphan Products Division (1 RO1FD004147). The Research Electronic Data Capture database is supported by National Institutes of Health Cooperative Agreement UL1TR001442. The Persyst EEG software company worked closely with the authors on the NEOLEV2 study and provided their software to the researchers free of charge, but have had no input into this article. The CortiCare commercial EEG monitoring company worked closely with the authors on the NEOLEV2 study on a commercial basis. They have had no input into the writing of this article. The authors of this article discussed the use of the automated neonatal seizure detection algorithm created by the Persyst EEG software company, which is not yet US Food and Drug Administration–approved for commercial use. Funded by the National Institutes of Health (NIH)." The authors reported not having potential conflicts of interest to disclose.

Solanki 2015

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (quote:) "All neonates who clinically developed their first seizure before 28 days of life". Exclusion criteria: (quote:) "Neonates already on ventilator support, or neonates with hypoglycaemia, hypocalcaemia and hypo/hypernatraemia, who responded to specific treatment (e.g. with glucose, calcium, etc.)". ***PB group*** Number of participants: 35 Gestation age (mean): 36.5 weeks Sex, %: male 71.4 (n = 25) Mean weight (kg): 2.4 Median age days: 1 Term/preterm (%): 77 (n = 27)/23 (n = 8) Religion Hindu/Muslim (%): 94 (n = 33)/6 (n = 2) Apgar score at 5 minutes (mean): 6.1 Perinatal asphyxia (%): 57 (n = 20) ***PHT group*** Number of participants: 35 Gestation age (mean): 36.6 weeks Sex, %: male 60 (n = 21) Mean weight (kg): 2.6 Median age days: 1 Term/preterm (%): 83 (n = 29)/17 (n = 6) Religion Hindu/Muslim (%): 91 (n = 32)/9 (n = 2) Apgar score at 5 minutes (mean): 4.9 Perinatal asphyxia (%): 85 (n = 28) ***Lorazepam group*** Number of participants: 36 Gestation age (mean): 35.6 weeks Sex, %: Male 63.9 (n = 23) Mean weight (kg): 2.3 Median age days: 1 Term/preterm (%): 70 (n = 25)/30 (n = 11)

Solanki 2015 *(Continued)*

	Religion Hindu/Muslim (%): 72 (n = 26)/28 (n = 10) Apgar score at 5 min (mean): 6.7 Perinatal asphyxia (%): 53 (n = 15) The study was conducted at a single neonatal intensive care unit in Bhavnagar, India, between August 2013 and July 2014.
Interventions	(Quote:)"The neonates were randomly assigned (single-blinded) to different treatments according to a block design to ensure balanced treatment assignment." (no further details are provided). PB (20 mg/kg), lorazepam (0.05 mg/kg) or PHT (20 mg/kg) administered intravenously (IV) over a 5-minute period. (Quote:) "If clinical seizures resumed after therapy had been discontinued, the attending physician decided whether to use another ASM. The heart rate and rhythm, mean blood pressure, and respiratory status were monitored continuously during treatment." No further details were provided.
Outcomes	(Quote:) "Complete control of seizures, within 2.5 min of starting a single dose ASM therapy, as determined by a physician". (Quote:) "Treatment was considered to have failed if the neonate had an episode of seizures lasting longer than 5 min or a total of 2.5 min of seizure activity within 5-min period after a single dose".
Notes	There was no external funding. The authors reported not having potential conflicts of interest to disclose.

Soul 2021

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (quote:) "neonates at postmenstrual age 34 to 44 weeks if they had clinically suspected or EEG-proven (i.e. confirmed) seizures, or were at high risk for developing seizures caused by hypoxic–ischaemic encephalopathy (HIE), focal stroke, ICH, acute meningoencephalitis, brain malformation, or a suspected/known genetic disorder." Exclusion criteria: (quote:) "neonates with seizures caused by transient metabolic abnormalities or inborn errors of metabolism; neonates who had received bumetanide, furosemide, phenytoin, or ≥ 40 mg/kg PB; neonates with total bilirubin > 15 mg/dL; and neonates treated with extracorporeal membrane oxygenation or at risk of imminent death" ***0.1 mg/kg bumetanide, 7 patients*** Male sex, n (%): 3 (34) Gestational age at birth, wk, median (IQR): 39 (38, 40) Birth weight, kg, median (IQR): 3.4 (3.1-3.8) *Race* Caucasian, n (%): 6 (86) Asian, n (%): 0 Unreported, n (%): 1 (14)

Soul 2021 *(Continued)*

Hispanic or Latino ethnicity, n (%): 1 (14)

Seizure aetiology

Hypoxic ischaemic encephalopathy, n (%): 3 (43)

Stroke, n (%): 4 (57)

Intracranial haemorrhage, n (%): 0

Other, n (%): 0

Therapeutic hypothermia, n (%): 3 (43)

0.2 mg/kg bumetanide, 15 patients

Male sex, n (%): 10 (67)

Gestational age at birth, wk, median (IQR): 40 (38-41)

Birth weight, kg, median (IQR): 3.4 (3.1- 3.8)

Race

Caucasian, n (%): 13 (87)

Asian, n (%): 1 (7)

Unreported, n (%): 1 (7)

Hispanic or Latino ethnicity, n (%): 1 (7)

Seizure aetiology

Hypoxic ischaemic encephalopathy, n (%): 7 (47)

Stroke, n (%): 3 (20)

Intracranial haemorrhage, n (%): 2 (13)

Other, n (%): 03 (20)

Therapeutic hypothermia, n (%): 4 (27)

0.3 mg/kg bumetanide, 5 patients

Male sex, n (%): 1 (20)

Gestational age at birth, wk, median (IQR): 39 (39, 39)

Birth weight, kg, median (IQR): 3.0 (2.9-3.3)

Race

Caucasian, n (%): 4 (80)

Asian, n (%): 0

Unreported, n (%): 1 (20)

Hispanic or Latino ethnicity, n (%): 0

Seizure aetiology

Hypoxic ischaemic encephalopathy, n (%): 4 (80)

Stroke, n (%): 0

Soul 2021 *(Continued)*

	Intracranial haemorrhage, n (%): 1 (20) Other, n (%): 0 Therapeutic hypothermia, n (%): 3 (60) ***Control, 16 patients*** Male sex, n (%): 7(44) Gestational age at birth, wk, median (IQR): 39.5 (39, 41) Birth weight, kg, median (IQR): 3.3 (3.0-3.5) *Race* Caucasian, n (%): 12 (75) Asian, n (%): 1 (6) Unreported, n (%): 3 (19) Hispanic or Latino ethnicity, n (%): 4 (25) *Seizure aetiology* Hypoxic ischaemic encephalopathy, n (%): 8 (50) Stroke, n (%): 0 Intracranial haemorrhage, n (%): 4 (25) Other, n (%): 4 (25) Therapeutic hypothermia, n (%): 5 (31) The study was conducted at 4 neonatal intensive care units in Boston, USA. Patients were enrolled from 2010 to 2017.
Interventions	Subjects were randomised if an EEG-proven seizure (confirmed by a study paediatric neurophysiologist) occurred at least 30 minutes after a loading dose of ≥ 20 to < 40 mg/kg phenobarbital. (Quote:) "bumetanide doses of 0.1, 0.2, and 0.3 mg/kg in comparison to a control group (normal saline), given in conjunction with 5 to 10 mg/kg phenobarbital (bumetanide + phenobarbital vs saline + phenobarbital). The choice of 5 or 10 mg/kg phenobarbital was at the discretion of the treating physician; doses and levels were the same in the control and bumetanide groups".
Outcomes	Determination of the pharmacokinetics and safety of bumetanide as add-on therapy to treat neonatal seizures An exploratory endpoint was the effect of bumetanide dose and exposure on seizure burden.
Notes	Funding: Quote: "The trial was funded by NIH National Institute of Neurological Disorders and Stroke grant 5R01 NS066929, and grants from the CURE foundation, Harvard Catalyst–Harvard Clinical and Translational Science Center, Charles H. Hood Foundation, Translational Research Program at Boston Children's Hospital, and Mooney Family Initiative for Translation and Clinical Studies in Rare Diseases. Tufts Clinical and Translational Science Institute (CTSI), UL1 TR001064." The authors reported not having potential conflicts of interest to disclose.

Srinivasakumar 2015

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (quote:) "1. ≥ 36 weeks' gestation at delivery; 2. Admitted to the NICU within the first 24 hours of life; and 3. Either fulfilled clinical criteria for moderate-to-severe HIE (Eunice Kennedy Shriver National Institute of Child Health and Human Development criteria) or had clinical seizures (suspected or confirmed)." Exclusion criteria: (quote:) "1. Neonates < 36 weeks' gestation; 2. > 24 hours of age (to exclude non-HIE causes of seizures); 3. Infants with congenital anomalies of the central nervous system; 4. Moribund infants for whom no further aggressive treatment is planned; 5. Infants who demonstrated electrographic SE at the beginning of the cEEG study (initial 1 hour cEEG)". ***Treatment of electrographic seizures group*** Gestational age, mean ± SD: wk 38.3 ± 2 Birth weight, mean ± SD: g 3233 ± 585 Gender, boy:girl %: 60:40 5-min Apgar Score: 4 Cord/first pH, mean ± SD: 7.05 ± 0.1 Inborn versus outborn, %: 40:60 Severity of HIE, moderate:severe: % 67:33 Abnormality on brain MRI: % 66 Therapeutic hypothermia: % 66 Age at start of cEEG monitoring, mean ± SD: h 12.5 ± 9.5 Electrographic SE: % 33 Duration of cEEG monitoring, mean ± SD: h 72.1 ± 37 ***Treatment of clinical seizures group*** Gestational age, mean ± SD: wk 38.5 ± 2 Birth weight, mean ± SD: g 3057 ± 602 Gender, boy:girl: % 60:40 5-min Apgar Score: 4 Cord/first pH, mean ± SD: 7.08 ± 0.2 Inborn versus outborn: % 40:60 Severity of HIE, moderate:severe: % 70:30 Abnormality on brain MRI: % 85 Therapeutic hypothermia: % 65 Age at start of cEEG monitoring, mean ± SD: h 13.3 ± 10.1 Electrographic SE: % 20 Duration of cEEG monitoring, mean ± SD: h 69.5 ± 31

Srinivasakumar 2015 *(Continued)*

	The study was conducted at a single centre in the USA from 2007 to 2011.
Interventions	Treatment of electrographic seizures alone versus treatment of clinical seizures ***Treatment of electrographic seizures*** Seizures were defined as (quote:) “rhythmic spike wave activity” lasting for > 10 seconds. Any EEG event, confirmed to be a seizure, with or without a clinical correlate lasting > 30 seconds, or more than 2 confirmed events detected by the algorithm in a 24-hour period were thresholds to commence standardised ASM treatment. Treatment consisted of a stepwise approach: PB 20 mg/kg (first-line); PB 20 mg/kg (second-line, if seizures continued); fosphenytoin 20 mg/kg (third-line, if seizures continued); if seizures continued: midazolam bolus 0.05 mg/kg followed by infusion at 0.15 mg/kg per hour for 24 hours, with decrease of dose to 0.1 mg/kg per hour for 24 hours and then to 0.05 mg/kg per hour for 24 hours before stopping. ***Treatment of clinical seizures*** Seizure diagnosis and treatment was based solely on clinical observation and was based on the following protocol: PB 20 mg/kg (first-line); PB 20 mg/kg (second-line, if seizures continued); fosphenytoin 20 mg/kg (third-line, if seizures continued); if seizures continued: midazolam bolus 0.05 mg/kg followed by infusion at 0.15 mg/kg per hour for 24 hours, with decrease of dose to 0.1 mg/kg per hour for 24 hours and then to 0.05 mg/kg per hour for 24 hours before stopping. (Quote:) "Neonates who developed electrographic SE, detected by the study epileptologist, in this group were unblinded and treated as in the electrographic seizures group".
Outcomes	Primary outcome: seizure burden Other outcomes: neurodevelopmental development at 18 to 24 months evaluated using the BSID III
Notes	The study was funded by the Thrasher Foundation. The authors reported not having potential conflicts of interest to disclose.

Susnerwala 2022

Study characteristics	
Methods	Randomised controlled trial, not blinded, 'pragmatic'. Randomisation via a computer-generated random number. The study was conducted at a tertiary care neonatal intensive care unit in Aurangabad, India. Patients were recruited between January 2019 and April 2020.
Participants	Neonates with clinical seizures presenting before 48 hrs with movements considered abnormal and lasting longer than 30s.
Interventions	LEV group: LEV 20 mg/kg IV, if seizures controlled, maintenance with 10 mg/kg BID. If seizures not controlled within 20 min, add-on of PB 20 mg/kg, followed by maintenance of 5 mg/kg*d PB group: PB 20 mg/kg IV, if seizures controlled, maintenance with 5 mg/kg*d. If seizures not controlled within 20 min, add-on of LEV 20 mg/kg Third-line PHT or midazolam for both groups

Susnerwala 2022 *(Continued)*

Outcomes	Primary outcome measure: clinical cessation of abnormal movements after loading for at least 24 hrs
Notes	103 neonates screened, 82 randomised (44 LEV, 38 PB). Mean age at enrolment 4.8 hrs. Clonic seizures in 51.2%. Primary outcome achieved in the LEV group in 29/44 vs 13/38 in the PB group. Secondary seizure control after adding LEV in 22/25 in the PB group vs 14/15 in the LEV group. Children receiving therapeutic hypothermia and erythropoietin included No serious adverse events reported, but higher mortality in PB group (21% vs 9%) EEG not considered feasible No information on conflicts of interest and funding was included in the manuscript.

Van Rooji 2010

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: (quote:) "gestational age of ≥ 37 weeks, admission to 1 of the NICUs 24 hours after birth, and diagnosis of HIE and neonatal seizures. HIE was defined on the basis of meeting ≥ 3 of the following criteria: (1) signs of intrauterine asphyxia (i.e. late decelerations on foetal electrocardiograms or meconium-stained liquor), (2) arterial cord blood pH of < 7.10, (3) delayed onset of spontaneous respiration, (4) Apgar score of ≤ 5 at 5 minutes, or (5) multiorgan failure (elevated liver enzyme levels, reduced diuresis, and cardiovascular problems)." Exclusion criteria: (quote:) "presence of congenital or chromosomal abnormalities, maternal use of narcotics or sedatives, treatment with phenytoin before referral, and administration of muscle-relaxing drugs." "Subclinical status epilepticus at the beginning of the aEEG registration". ***Treatment of both clinical seizures and subclinical seizure patterns (group A)*** Gestational age, mean SD: wk 39.5 ± 1.8 Birth weight, mean SD: g 3254 ± 701 Gender, n (%): male 8 (42); female: 11 (58) Outborn, n (%): 17 (90) Apgar score at 5 min of 5, n (%): 12 (67) Cord pH, mean (range) (group A, N = 12): 6.87 (6.67 to 7.00) Lactate level, mean (range), mmol/L (group A, N = 15): 14.1 (2.2 to 26) *HIE, n (%)* Grade II: 11 (58) Grade III: 8 (42) *Mode of delivery, n (%)* Vaginal: 3 (16) Ventouse extraction: 2 (10)

Van Rooji 2010 *(Continued)*

	Caesarean section, emergency: 14 (74) Meconium-stained liquor, n (%): 9 (47) Mechanical ventilation, n (%): 15 (79) ***Blinding of the aEEG registration and treatment of clinical seizures only (group B)*** Gestational age, mean SD: wk 39.9 ± 1.3 Birth weight, mean SD: g 3416 ± 487 Gender, n (%): male 7 (50); female 7 (50) Outborn, n (%): 12 (86) Apgar score at 5 min of 5 n (%): 11 (79) Cord pH, mean (range) (group B, N = 11): 6.88 (6.64 to 7.30) Lactate level, mean (range), mmol/L (group B, N = 13): 9.3 (3.1 to 29.0) *HIE, n (%)* Grade II: 7 (50) Grade III: 7 (50) *Mode of delivery, n (%)* Vaginal: 4 (29) Ventouse extraction: 3 (21) Caesarean section, emergency: 7 (50) Meconium-stained liquor, n (%): 7 (50) Mechanical ventilation, n (%): 13 (93) The multicentre study was conducted at eleven perinatal centres in the Netherlands and Belgium between November 2003 and April 2008.
Interventions	Treatment of both clinical seizures and subclinical seizure patterns (group A) versus blinding of the aEEG registration and treatment of clinical seizures only (group B) In both groups, the treatment consisted of the following protocol: First-line: PB: 20 mg/kg, eventually another 10 mg/kg Second-line: midazolam: loading dose of 0.05 mg/kg, followed by continuous infusion of 0.15 mg/kg per h, to maximum of 0.2 mg/kg per hour (when seizures have been stopped for 24 hours, tapered to 0.1 mg/kg per h and stopped after 48 hours) Third-line: lidocaine: loading dose of 2 mg/kg, followed by continuous infusion of 6 mg/kg per h for 6 hours, then 4 mg/kg per h for 12 hours, and then 2 mg/kg per hour for 12 hours (always stopped after 36 hours) Fourth-line: clonazepam: loading dose of 0.1 mg/kg, followed by continuous infusion of 0.1 to 0.5 mg/kg per day Fifth-line: pyridoxine: 50 mg/kg Sixth-line: further treatment on the basis of clinician's decisions
Outcomes	Primary outcome: reduction of the total duration of seizures detected on aEEG

Van Rooji 2010 *(Continued)*

	Other outcomes: degree of brain injury seen on MRI scans. These were obtained 4 to 10 days after birth and retrospectively reviewed and scored by 2 investigators blinded to aEEG results.
Notes	Funding: Dr van Rooji was supported by the Dutch Epilepsy Foundation (grant NEF 3-15). Interests: not mentioned in the publication

aEEG: amplitude-integrated electroencephalography;**AGA**: appropriate for gestational age; **ASM**: anti-seizure medication; **BSID**: Bayley Scales of Infant Development; **cEEG**: continuous electroencephalography; **CNS**: central nervous system; **EEG**: electroencephalography; **GE**: genetic epilepsy;**HIE**: hypoxic-ischaemic encephalopathy; **HNNE**: Hammersmitz Neurological Neonatal Neurological Examination; **ICH**: intracranial haemorrhage; **IEM**: inborn error of metabolism;**IQR**: inner-quartile range; **IUI**: intrauterine infections;**IV**: intravenous; **LEV**: levetiracetam; **LGA**: large for gestational age; **LSCS**: lower segment caesarean section; **MRI**: magnetic resonance imaging; **NICU**: neonatal intensive care unit; **NS**: normal saline; **NVD**: normal vaginal delivery; **PB**: phenobarbitone; **PIH**: pregnancy-induced hypertension; **PHT**: phenytoin; **PROM**: premature rupture of membranes;**SD**: standard deviation; **SE**: structural epilepsy; **SGA**: small for gestational age.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abend 2011	Retrospective cohort study (on levetiracetam for neonatal seizures)
Arican 2020	Cross-sectional study (comparing the neurocognitive outcomes of neonates who were treated with levetiracetam or phenobarbitone)
Castro Conde 2005	Prospective cohort study (evaluating midazolam as a third-line drug)
Deshmukh 1986	Case series (on 7 neonates treated with lorazepam as a third-line drug)
Dwivedi 2019	Retrospective cohort study (to examine the factors associated with failure of phenobarbitone as first-line ASM in HIE)
Favié 2020	Observational study (evaluating the pharmacokinetics of lignocaine in neonates)
Gal 1988	Case series (of 6 neonates treated with valproic acid)
Glass 2021	Prospective cohort study (comparing maintenance ASM versus no maintenance ASM on neurodevelopment and epilepsy at 24 months)
Han 2018	Retrospective study (on levetiracetam as first-line ASM)
Hellström-Westas 1988	Observational study (evaluating lignocaine in neonatal seizures)
Hu 2003	This prospective open-label study was designed to determine the efficacy and safety of continuous midazolam infusion in neonates with uncontrollable neonatal seizures. Patients whose seizures could not be controlled by diazepam, phenytoin or phenobarbital were enrolled.
Hunt 2021	This RCT on treating both clinical and electrographic seizures versus treating clinical seizures alone has included neonates with and without electrographic seizures. Data on outcomes of only those neonates who had electrographic seizures were not available.
Jawadekar 1992	Prospective observational study (evaluating phenobarbitone and phenytoin)
Jayswal 2021	Prospective cohort study (comparing midazolam versus levetiracetam as third-line ASM)
Kanmaz 2021	Retrospective observational study (on levetiracetam as first-line ASM)

Study	Reason for exclusion
Liu 2020	Retrospective study (comparing phenobarbitone and levetiracetam as first-line ASM)
Low 2016	Prospective observational study (evaluating phenobarbitone for EEG-confirmed seizures)
Maitre 2013	Retrospective cohort study (comparing the effect of levetiracetam and phenobarbitone on neurodevelopmental outcomes)
Mollamohammadi 2018	Single-arm study evaluating levetiracetam as a third-line drug
Pressler 2015	This open-label study without control group aimed to assess dose and feasibility of intravenous bumetanide as an add-on to phenobarbital for treatment of neonatal seizures.
Ramantani 2011	Prospective observational study (evaluating levetiracetam as first-line ASM)
Rao 2018	Retrospective cohort study (comparing levetiracetam and phenobarbitone as first-line ASM in HIE)
Rochefort 1989	Conference abstract. We did not have adequate information for risk of bias assessment and adequate data on outcomes.
Sedighi 2016	Single-arm study (evaluating levetiracetam as first-line ASM)
Shany 2007	Retrospective cohort study (comparing lignocaine and midazolam as second-line ASM)
Thibault 2020	Retrospective cohort study (comparing levetiracetam and phenobarbitone as first-line ASM in seizures following neonatal cardiac surgery)
Verwoerd 2022	Retrospective cohort study (comparing levetiracetam and phenobarbitone as first-line ASM)
Wagner 2021	Retrospective cohort study (comparing levetiracetam and phenobarbitone as first-line ASM)
Weeke 2016	Retrospective observational study (evaluating lignocaine in neonatal seizures)
Yamamoto 2007	Retrospective cohort study (comparing lignocaine and midazolam in neonatal status epilepticus)

ASM: anti-seizure medication; **EEG**: electroencephalography; **HIE**: hypoxic-ischaemic encephalopathy; **RCT**: randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Gyandeep 2023

Methods	Randomised controlled trial
Participants	Preterm neonates born between 28 and 36 weeks' gestational age with clinical seizures
Interventions	Intervention 1 - Phenobarbitone as first-line ASM Intervention 2 - Levetiracetam as first-line ASM
Outcomes	Primary outcome - cessation of clinical seizure and remaining seizure-free for next 24 h Other outcome - adverse events of ASMs such as apnoea, increase in respiratory support and hypotension
Notes	This is the only RCT including ASM in preterm neonates with seizures.

Gyandeep 2023 *(Continued)*

	The study is awaiting classification, as we need additional data from the study authors to classify the study and include in the appropriate meta-analysis.

Mohammadi 2023

Methods	Randomised controlled trial
Participants	Term neonates with seizures
Interventions	Intervention 1 - Levetiracetam as second-line ASM Intervention 2 - Phenytoin as second-line ASM
Outcomes	Cessation of seizures, adverse effects of the drug
Notes	Method of diagnosing seizures (clinical or EEG-based) was not mentioned. Seizure control (time-line) was not defined. The study is awaiting classification, as we need additional data from the study authors to classify the study and include in the appropriate meta-analysis.

ASM: antiseizure medication; **EEG**: electroencephalogram

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12622000470796

Study name	EFFICACY AND SAFETY OF levetiracetam versus phenytoin for neonatal seizures. A randomized controlled trial
Methods	
Participants	Neonates up to 30 days of life presenting with seizures
Interventions	Levetiracetam loading dose 5-10 mg/kg IV over 15 min, maintenance 10 mg/kg IV 12-hourly
Outcomes	Clinical termination of seizures
Starting date	Not given
Contact information	drkamo50@gmail.com
Notes	No information on randomisation protocol; no information on phenytoin treatment protocol

CTRI/2013/01/003310

Study name	Comparison of levetiracetam with phenobarbitone in neonatal seizures
Methods	RCT
Participants	Neonates with clinical seizures
Interventions	LEV 60 mg/kg vs PB 20-30 mg/kg

CTRI/2013/01/003310 *(Continued)*

Outcomes	Control of clinical seizures, adverse events, neurodevelopment
Starting date	2012
Contact information	anuamit7@rediffmail.com
Notes	Calculated sample size 80; no further entries; no entry in MEDLINE

CTRI/2013/04/003585

Study name	Levetiracetam for management of seizures in newborn
Methods	Not specified
Participants	Neonates > 30 w and 1.5 kg with clinical or electrographic seizures
Interventions	LEV 20 mg/kg vs PB 20 mg/kg, maintenance
Outcomes	Not specified
Starting date	2012
Contact information	rabindranindia@yahoo.co.in
Notes	Calculated sample size 100; last entry 2013

CTRI/2014/06/004659

Study name	Levetiracetam vs phenobarbitone for the control of neonatal seizures: a double-blind randomised controlled trial
Methods	RCT
Participants	Neonates (> 32 weeks) with clinical seizures
Interventions	LEV 20-60 mg/kg, vs PB 20-40 mg
Outcomes	Time until seizure control, mortality, mortality, neurodevelopment at 18 months, adverse events (not specified)
Starting date	2014
Contact information	skb.bmc@gmail.com
Notes	Expected sample size 300; entry last updated 2014

CTRI/2015/06/005849

Study name	Levetiracetam vs phenobarbitone in acute neonatal seizures

CTRI/2015/06/005849 *(Continued)*

Methods	RCT
Participants	Neonates > 1000 g and > 28 weeks
Interventions	LEV 30-40 mg/kg vs PB 20-30 mg/kg
Outcomes	Recurrence of seizures, need for further ASM, adverse events, mortality, neurodevelopmental outcome
Starting date	2013
Contact information	drnikhilkulkarni83@gmail.com
Notes	Estimated sample size 32, apparently 38 achieved, completed, no results published

CTRI/2016/10/007412

Study name	A clinical study to compare levetiracetam and phenobarbitone in newborns with birth asphyxia
Methods	RCT
Participants	Term neonates with HIE II/III, age < 24 hours
Interventions	PB 20 mg/kg, maintenance vs LEV 20-60 mg/kg, maintenance
Outcomes	Seizure control with 1st-line drug, need for further ASM, neonatal mortality, adverse events of LEV, duration of hospital stay, neurodevelopment
Starting date	2016
Contact information	sha.akht@gmail.com
Notes	Calculated sample size 60

CTRI/2018/04/013161

Study name	Levetiracetam used as first-line anti-epileptic versus phenobarbitone in neonatal convulsions
Methods	RCT, add-on if required
Participants	Neonates with clinical seizures
Interventions	LEV 20-40 mg/kg, maintenance vs PB 20-30 mg/kg, maintenance
Outcomes	Cessation of seizures, recurrence at 24 hours, need for further ASM, adverse events, absence of seizures at 48 hours, adverse events
Starting date	2014
Contact information	zyee08@gmail.com
Notes	Sample size 100, achieved, reported that LEV more efficient than PB; no PubMed listing

CTRI/2020/03/023961

Study name	A randomized controlled trial of levetiracetam vs phenobarbitone for treatment of neonatal seizures
Methods	RCT
Participants	Neonates (35-42 weeks) with seizures
Interventions	PB 20-30 mg/kg vs LEV 20-30 mg
Outcomes	Seizure control within 1 hour, recurrence of seizures, adverse events (respiratory depression, heart rate fluctuation, duration of hospitalisation)
Starting date	2020
Contact information	manikant7@yahoo.com
Notes	Estimated sample size 90, EEG not specified

CTRI/2021/02/031290

Study name	Comparison between phenobarbitone and levetiracetam as the initial anti convulsant in treating preterm neonatal seizures
Methods	RCT
Participants	Neonates < 37 weeks with clinical seizures
Interventions	PB 15 mg/kg vs LEV 40 mg/kg
Outcomes	Cessation of seizures at 24 hours, clinical response based on seizure aetiology at 1 month
Starting date	2021
Contact information	doc.sant@yahoo.co.in
Notes	Calculated sample size 106

CTRI/2022/09/045658

Study name	To compare the effect of two anticonvulsant drugs levetiracetam and phenobarbitone in neonates with seizures
Methods	Randomised controlled trial
Participants	Neonates with clinical seizures not controlled after correction of hypoglycaemia and hypocalcaemia
Interventions	Intervention1: Levetiracetam [LEV]: loading with LEV 20 mg/kg IV in neonates with seizures: if seizures stop, put on maintenance dose @ 20 mg/kg/day; if seizures continue, reload with LEV 20 mg/kg followed by maintenance dose of 40 mg/kg/day; if seizures still persist, switch over to phenobarbitone.

CTRI/2022/09/045658 *(Continued)*

	Control Intervention1: Phenobarbitone [PB]: loading with PB 20 mg/kg IV in neonates with seizures: if seizures stop, put on maintenance dose @ 3 mg/kg/day; if seizures continue, reload with PB 10 mg/kg followed by maintenance dose of 5 mg/kg/day; if seizures still persist, switch over to levetiracetam
Outcomes	Cessation of seizures within 48 hours of administration of first or second loading dose of the drug [levetiracetam vs phenobarbitone], time point: 48 hours
Starting date	2021
Contact information	drmanisha99@yahoo.com
Notes	Clinical diagnosis of seizures and evaluation of treatment success

CTRI/2023/02/049794

Study name	Study comparing efficacy of two drugs as first line drug in late preterm and term babies with neonatal seizure
Methods	Randomised controlled trial
Participants	Term and preterm neonates apparently presenting with seizures (clinical diagnosis) lasting 3 min or more
Interventions	Intervention 1: Levetiracetam: Injection of levetiracetam (40 mg/kg then 20 mg/kg) as 1st-line drug in neonatal seizures given over 20 minutes Control intervention 1: Phenobarbitone: Injection of phenobarbitone (20 mg/kg then 20 mg/kg) loading dose is the standard 1st-line drug for neonatal seizures given over 20 minutes
Outcomes	Termination of clinical seizures (seizure control in 60 minutes and no further seizure in 24 hours). Time point: Termination of clinical seizures (seizure control in 60 minutes and no further seizure in 24 hours)
Starting date	
Contact information	bhupendra.gupta@tatasteel.com
Notes	Clinical diagnosis of seizures and assessment of treatment success

IRCT2014070318334N1

Study name	Study of levetiracetam effect in reduction of seizure frequency in neonates with seizure
Methods	Observational, uncontrolled
Participants	Neonates > 34 weeks and > 1999 g, clinical seizures
Interventions	Levetiracetam 10 mg/kg every 12 hours for 3 months
Outcomes	Seizure frequency at 4 weeks, seizure duration at 4 weeks, adverse events
Starting date	2014

IRCT2014070318334N1 *(Continued)*

Contact information	m.sedighi@kums.ac.ir
Notes	Calculated sample size 50; no further entries

IRCT20160523028008N23

Study name	The effect of levetiracetam and phenobarbital on the control of neonatal seizures
Methods	Randomised controlled trial
Participants	Term neonates with seizures (clinical diagnosis)
Interventions	Intervention 1: Intervention group: Patients are treated with levetiracetam injection (500 mg/5 mL by Estragen Company, Switzerland) at a loading dose of 50 mg/kg and infusion rate of 2 mg/kg/min (within 10 cc of normal saline) under cardiorespiratory monitoring. If seizures continue with the first dose of levetiracetam, the drug is re-loaded at a dose of 50 mg/kg at the same infusion rate (within 10 cc of normal saline). If the seizure does not stop or returns after 15 minutes, even after the second dose of medication, the treatment groups are changed. If the seizure does not stop or returns after 15 minutes after changing treatment groups, other anticonvulsant drugs are used. Intervention 2: Control group: Patients in the control group are treated with phenobarbital injection (200 mg/mL from Chemidarou company) at a loading dose of 20 mg/kg and at an infusion rate of 1 m/kg/min (within 10 cc of normal saline) under cardiorespiratory monitoring. If the seizure continues with the first dose, phenobarbital is re-loaded by infusion at a dose of 20 mg per kg at the same rate as before. If the seizure does not stop or returns after 15 minutes, even after the second dose of medication, the treatment groups are changed. If the seizure does not stop or returns after 15 minutes after changing treatment groups, other anticonvulsant drugs are used.
Outcomes	Complete cessation of seizures for 24 hours after medication. Time point: in the first 24 hours after medication. Method of measurement: stopping seizure movements clinically (clinical assessment Number of doses received to stop seizures. Time point: in the first 24 hours after medication. Method of measurement: patient medical record
Starting date	
Contact information	naderfaraji59@gmail.com
Notes	Clinical diagnosis of seizures and assessment of treatment success

IRCT20190526043717N1

Study name	Comparison of intravenous levetiracetam and phenobarbital for management of neonatal seizures
Methods	RCT, double-blind
Participants	Neonates and infants > 37 weeks and > 2500 g up to 1 year of age with clinical seizures
Interventions	LEV 20-40 mg/kg, maintenance vs PB 20-30 mg/kg in 2 doses
Outcomes	Clinical seizures at 24 hours, recurrence of clinical seizures until 3 months after the intervention
Starting date	2019

IRCT20190526043717N1 *(Continued)*

Contact information	masoumeh-hospital@muq.ac.ir
Notes	Calculated sample size 100; neonates and infants

IRCT20200115046137N1

Study name	Comparison of the effects of phenobarbital, topiramate and levetiracetam in the treatment of neonatal seizures
Methods	RCT, single-blind
Participants	Neonates with clinical seizures
Interventions	PB 5 mg in 2 doses, TPM 3 mg in 2 doses, LEV 20 mg in 2 doses
Outcomes	Seizures every month
Starting date	2020
Contact information	samiei.moh@gmail.com
Notes	Calculated sample size 60; no further entries

IRCT20200131046317N3

Study name	Comparison of the effects of phenobarbital and levetiracetam on neonatal seizures after discharge
Methods	RCT, double-blind
Participants	Term neonates with clinical seizures
Interventions	LEV 30 mg/kg*d maintenance for 3/6 months vs PB 5 mg/kg*d for 3/6 months
Outcomes	Growth at 3 and 6 months, recurrence of seizures at 3 and 6 months
Starting date	2021
Contact information	dr.nazanin_zand@yahoo.com
Notes	Calculated sample size 60; seizure diagnosis not specified

IRCT20200528047589N1

Study name	Comparison of effects of phenobarbital and levetiracetam in the control of neonatal seizures
Methods	RCT, double-blind
Participants	Neonates (> 33 weeks, > 2 kg), clinical seizures
Interventions	LEV 30-50 mg/kg vs PB 20-30 mg/kg

IRCT20200528047589N1 *(Continued)*

Outcomes	Cessation of clinical seizures, ASM continuation at discharge
Starting date	2020
Contact information	MaamouriGh@mums.ac.ir
Notes	Estimated sample size 74

IRCT20220619055221N1

Study name	Efficacy of levetiracetam compared to intravenous phenytoin in treatment of acute phase of neonatal seizure
Methods	Randomised controlled trial
Participants	Patients diagnosed with neonatal seizures
Interventions	Levetiracetam 20 mg/kg IV versus phenytoin 20 mg/kg IV
Outcomes	Seizure control and non-recurrence within 24 hours
Starting date	22/11/2022
Contact information	parvanehbabaey@gmail.com
Notes	Recruitment complete

NCT01089504

Study name	Prophylactic phenobarbital after neonatal seizures (PROPHENO)
Methods	RCT
Participants	Neonates (> 33 weeks), neonatal seizures (clinical or electrographic or electroclinical)
Interventions	PB 4-5 mg/kg for 4 months vs placebo
Outcomes	Bayley at 18-22 m, seizure recurrence
Starting date	2016
Contact information	ronnie_guillet@urmc.rochester.edu
Notes	Terminated in 2016 due to inadequate recruitment

NCT02550028

Study name	Levetiracetam treatment of neonatal seizures
Methods	RCT

NCT02550028 *(Continued)*

Participants	Term neonates (> 2500 g) with seizures confirmed by EEG
Interventions	LEV orally 50 mg/kg, maintenance 30 mg/kg*d vs PB IV 20-40 mg/kg, maintenance 5 mg/kg*d
Outcomes	EEG (baseline) at 28 days, MRI, neurodevelopment, time to seizure control (days), adverse events
Starting date	2015
Contact information	zwhchfu@126.com
Notes	Calculated sample size 100, in last update 2021; no information if this was achieved

NCT03107507

Study name	Efficacy of levetiracetam in control of neonatal seizures guided by an EEG
Methods	RCT
Participants	Term neonates with seizures (confirmed by aEEG)
Interventions	LEV oral 40-50 mg/kg, maintenance vs PB IV 20-40 mg/kg, maintenance
Outcomes	Number of seizures, hours to achieve seizure control, dose escalation data on LEV, aEEG accuracy, effect of LEV on aEEG background activity, short-term outcome at 3 months
Starting date	2017
Contact information	yarasalah.shaheen@gmail.com
Notes	Estimated sample size not specified; no further entries

NCT04320940

Study name	Efficacy and safety of intravenous phenobarbital in neonatal seizures
Methods	RCT, double-blind
Participants	Neonates > 33 weeks with high probability of seizures, cEEG, seizures for at least 30 s/h
Interventions	PB 20/kg (if required plus 20) vs PB 40 mg/kg (if required plus 10)
Outcomes	No requirement of ASM after 1st dose PB at 24 hours; no requirement of ASM after 1st dose PB at 2 hours; no requirement of ASM after 2nd dose of PB; seizure burden
Starting date	2020
Contact information	rnoor@nemaresearch.net
Notes	Calculated sample size 490; very interesting study

NCT05291455	
Study name	Efficacy of lacosamide in neonatal status epilepticus: a randomised controlled study
Methods	RCT
Participants	Neonates with status epilepticus (not specified)
Interventions	LCM vs PB (doses not specified)
Outcomes	Cessation of seizures (not specified)
Starting date	2022
Contact information	abeersalamah84@yahoo.com
Notes	Estimated sample size not specified

aEEG: amplitude-integrated electroencephalography; **ASM**:antiseizure medication; **cc:** cubic centimetres; **cEEG**:continuous electroencephalography; **EEG**:electroencephalogram;; **HIE**:hypoxic-ischaemic encephalopathy; **IV**:intravenous; **LCM**: lacosamide; **LEV**: levetiracetam;**MRI**:magnetic resonance imaging; **PB**: phenobarbitone; **RCT**: randomised controlled trial; **s/h: ;TPM**:topiramate; **vs**: versus

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 Proportion of infants who achieve seizure control after the first loading dose of ASM

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sharpe 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.2 Proportion of infants who achieve seizure control after the the maximal loading dose of ASM

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sharpe 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.3 Mortality before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sharpe 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.4 Requirement for mechanical ventilation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sharpe 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.5 Proportion of infants who develop sedation or drowsiness

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sharpe 2020	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.6 Bradycardia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sharpe 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.7 Hypotension requiring volume or inotropes

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sharpe 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.8 Shock requiring volume or inotropes

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sharpe 2020	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.9 Recurrence of seizure before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sharpe 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.10 Proportion of infants with epilepsy post-discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sharpe 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.1 Proportion of infants who achieve seizure control after the first loading dose of ASM

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Akeel 2022	✓	✓	✓	~	~	✗
Gowda 2019	✓	✓	✓	✗	✓	✗
Susnerwala 2022	✓	✓	✓	~	✓	~

Risk of bias for analysis 2.2 Proportion of infants who achieve seizure control after the maximal loading dose of ASM

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ghaffar 2020	~	~	✓	✗	~	✗
Gowda 2019	✓	✓	✓	✗	✓	✗
Khan 2020	~	✓	✓	✗	~	✗

Risk of bias for analysis 2.3 Mortality before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Falsaperla 2019	~	✓	✓	✓	~	✗
Gowda 2019	✓	✓	✓	✓	✓	✓
Khan 2020	~	✓	✓	✓	~	✗
Perveen 2016	✓	✓	✓	✓	✓	✓
Prakash 2019	✓	✓	✓	✓	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Susnerwala 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.4 Requirement for mechanical ventilation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Akeel 2022	✓	✓	✓	✓	~	~
Falsaperla 2019	~	✓	✓	✓	~	✗
Gowda 2019	✓	✓	✓	✓	✓	✓
Khan 2020	~	✓	✓	✓	~	✗
Perveen 2016	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.5 Proportion of infants who develop sedation or drowsiness

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Khan 2020	~	✓	✓	✗	~	✗
Prakash 2019	✓	✓	✓	✗	~	✗

Risk of bias for analysis 2.6 Bradycardia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Akeel 2022	✓	✓	✓	✓	~	~
Falsaperla 2019	~	✓	✓	✓	~	✗
Gowda 2019	✓	✓	✓	✓	✓	✓
Khan 2020	~	✓	✓	✓	~	✗

Risk of bias for analysis 2.7 Hypotension requiring volume or inotropes

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Falsaperla 2019	~	✓	✓	✓	~	✗
Khan 2020	~	✓	✓	✓	~	✗

Risk of bias for analysis 2.8 Shock requiring volume or inotropes

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Falsaperla 2019	~	✓	✓	~	~	✗
Khan 2020	~	✓	✓	~	~	✗
Perveen 2016	✓	✓	✓	~	✓	~

Risk of bias for analysis 2.9 Proportion of infants with an abnormal background pattern in EEG during ASM treatment

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Falsaperla 2019	~	✓	✓	✓	~	✗

Risk of bias for analysis 2.10 Proportion of infants with an abnormal background pattern in EEG after stopping ASM

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Falsaperla 2019	~	✓	✓	✓	~	✗

Risk of bias for analysis 2.11 Duration of hospital stay

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Falsaperla 2019	~	✓	✓	✓	~	✗
Perveen 2016	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.12 Recurrence of seizure before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Falsaperla 2019	~	✓	✓	✗	~	✗
Khan 2020	~	✓	✓	✗	~	✗

Risk of bias for analysis 2.13 Proportion of infants with persistent seizures and/or requiring ASM at discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Falsaperla 2019	~	✓	✓	✗	~	✗

Risk of bias for analysis 2.14 Proportion of infants discharged on gavage feeds

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Falsaperla 2019	~	✓	✓	✓	~	✗
Khan 2020	~	✓	✓	✓	~	✗

Risk of bias for analysis 2.15 Proportion of infants with an abnormal neurological examination at discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Falsaperla 2019	~	✓	✓	~	~	✗
Khan 2020	~	✓	✓	~	~	✗
Perveen 2016	✓	✓	✓	~	✓	~
Susnerwala 2022	✓	✓	✓	✗	✓	✗

Risk of bias for analysis 2.16 Proportion of infants who develop epilepsy post discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Falsaperla 2019	~	✓	✓	✓	~	✗

Risk of bias for analysis 3.1 Proportion of infants who achieve seizure control after the maximal loading dose of ASM

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Painter 1999	~	✓	✓	✓	~	✗

Risk of bias for analysis 3.2 Arrythmias causing circulatory disturbance

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Painter 1999	~	✓	✓	✓	~	✗

Risk of bias for analysis 3.3 Hypotension requiring volume or inotropes

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Painter 1999	~	✓	✓	✓	~	✗

Risk of bias for analysis 3.4 Bradycardia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Painter 1999	~	✓	✓	✓	~	✗

Risk of bias for analysis 4.1 Proportion of infants who achieve seizure control after the first loading dose of ASM

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Pathak 2013	✓	✓	✓	~	✓	~
Solanki 2015	✗	✓	✓	~	✓	✗

Risk of bias for analysis 4.2 Mortality before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Pathak 2013	✓	✓	✓	✓	✓	✓
Solanki 2015	✗	✓	✓	✓	✓	✗

Risk of bias for analysis 4.3 Requirement of mechanical ventilation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Pathak 2013	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.4 Proportion of infants who develop sedation or drowsiness

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Solanki 2015	✗	✓	✓	~	✓	✗

Risk of bias for analysis 4.5 Bradycardia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Pathak 2013	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.6 Proportion of infants with persistent seizures and/or requiring ASM at discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Solanki 2015	✗	✓	✓	~	✓	✗

Risk of bias for analysis 5.1 Proportion of infants who achieve seizure control after the first loading dose of ASM

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Solanki 2015	✗	✓	✓	~	✓	✗

Risk of bias for analysis 5.2 Mortality before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Solanki 2015	✗	✓	✓	✓	✓	✗

Risk of bias for analysis 5.3 Proportion of infants who develop sedation or drowsiness

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Solanki 2015	✗	✓	✓	~	✓	✗

Risk of bias for analysis 5.4 Proportion of infants with persistent seizures and/or requiring ASM at discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Solanki 2015	✗	✓	✓	~	✓	✗

Risk of bias for analysis 6.1 Proportion of infants who achieve seizure control after the first loading dose of ASM

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Solanki 2015	✗	✓	✓	~	✓	✗

Risk of bias for analysis 6.2 Mortality before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Solanki 2015	✗	✓	✓	✓	✓	✗

Risk of bias for analysis 6.3 Proportion of infants who develop sedation or drowsiness

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Solanki 2015	✗	✓	✓	~	✓	✗

Risk of bias for analysis 6.4 Proportion of infants with persistent seizures and/or requiring ASM at discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Solanki 2015	✗	✓	✓	~	✓	✗

Risk of bias for analysis 7.1 Proportion of infants who achieve seizure control after the first loading dose of ASM

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Soul 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 7.2 Mortality before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Soul 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 7.3 Proportion of infants with cognitive impairment at 18-24 months

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Soul 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 7.4 Seizure burden during hospitalisation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Soul 2021	✓	✓	✓	✓	✓	~

Risk of bias for analysis 7.5 Requirement for mechanical ventilation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Soul 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 7.6 Hypotension requiring volume or inotropes

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Soul 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 7.7 Proportion of infants with an abnormal background pattern in EEG during ASM treatment

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Soul 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 7.8 Proportion of infants who develop epilepsy post discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Soul 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 8.2 Mortality or neurodevelopmental disability at 12 months' corrected age

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Boylan 2004	~	✓	✓	✓	~	✗

Risk of bias for analysis 8.3 Mortality before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Boylan 2004	~	✓	✓	✓	~	✗

Risk of bias for analysis 8.4 Neurodevelopmental disability at 12 months' corrected age

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Boylan 2004	~	✓	✓	✓	~	✗

Risk of bias for analysis 9.1 Proportion of infants with repeat seizure before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Jindal 2021	✓	✓	✓	✗	✓	✗
Saxena 2016	✓	✓	✓	✗	✓	✗

Risk of bias for analysis 9.2 Mortality before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Jindal 2021	✓	✓	✓	✓	✓	✓
Saxena 2016	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 9.3 Mortality at 18 to 24 months

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Saxena 2016	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 9.4 Neurodevelopmental disability at 18 to 24 months' corrected age

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Saxena 2016	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 9.5 Requirement for mechanical ventilation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Jindal 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 9.6 Shock requiring volume or inotropes

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Jindal 2021	✓	✓	✓	✓	✓	✓
Saxena 2016	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 9.7 Abnormal background pattern in EEG after achieving seizure control

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Saxena 2016	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 9.8 Duration of hospital stay

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Jindal 2021	✓	✓	✓	✓	✓	✓
Saxena 2016	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 9.9 Proportion of infants with persistent seizures and/or requiring ASM at discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Jindal 2021	✓	✓	✓	✗	✓	✗

Risk of bias for analysis 9.10 Abnormal neurological examination at discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Jindal 2021	✓	✓	✓	~	✓	~
Saxena 2016	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 9.11 Proportion of infants who develop epilepsy post-discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Saxena 2016	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 10.1 Seizure burden during hospitalisation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Srinivasakumar 2015	✓	✓	✓	✓	✓	✓
Van Rooji 2010	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 10.2 Mortality before hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Srinivasakumar 2015	✓	✓	✓	✓	✓	✓
Van Rooji 2010	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 10.3 Proportion of infants who develop epilepsy post-discharge

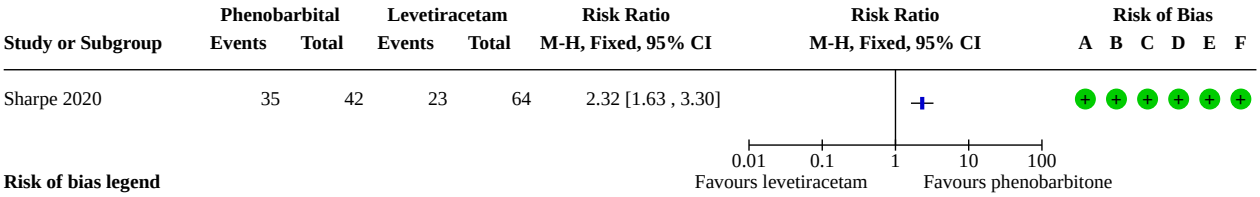
	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Srinivasakumar 2015	✓	✓	✓	✓	✓	✓

DATA AND ANALYSES

Comparison 1. Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Proportion of infants who achieve seizure control after the first loading dose of ASM	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2 Proportion of infants who achieve seizure control after the the maximal loading dose of ASM	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3 Mortality before hospital discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4 Requirement for mechanical ventilation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.5 Proportion of infants who develop sedation or drowsiness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6 Bradycardia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.7 Hypotension requiring volume or inotropes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8 Shock requiring volume or inotropes	1		Risk Ratio (M-H, Fixed, 99% CI)	Totals not selected
1.9 Recurrence of seizure before hospital discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.10 Proportion of infants with epilepsy post-discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

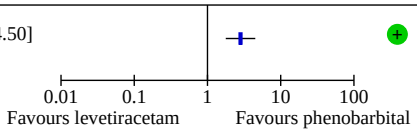
Analysis 1.1. Comparison 1: Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures, Outcome 1: Proportion of infants who achieve seizure control after the first loading dose of ASM



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures, Outcome 2: Proportion of infants who achieve seizure control after the the maximal loading dose of ASM

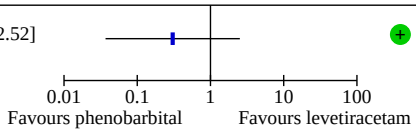
Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Sharpe 2020	24	30	15	53	2.83 [1.78 , 4.50]	+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures, Outcome 3: Mortality before hospital discharge

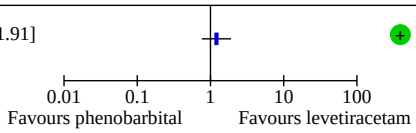
Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Sharpe 2020	1	42	5	64	0.30 [0.04 , 2.52]	+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures, Outcome 4: Requirement for mechanical ventilation

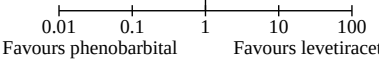
Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Sharpe 2020	19	42	24	64	1.21 [0.76 , 1.91]	+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures, Outcome 5: Proportion of infants who develop sedation or drowsiness

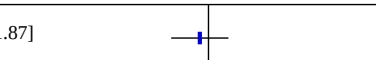
Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Sharpe 2020	8	42	7	64	1.74 [0.68 , 4.44]		+	+	+	?	+	?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures, Outcome 6: Bradycardia

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Sharpe 2020	6	42	12	64	0.76 [0.31 , 1.87]		+	+	+	+	+	+



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

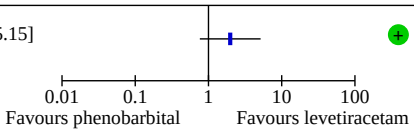
Analysis 1.7. Comparison 1: Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures, Outcome 7: Hypotension requiring volume or inotropes

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Sharpe 2020	7	42	3	64	3.56 [0.97 , 12.99]		+	+	+	+	+	+

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.8. Comparison 1: Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures, Outcome 8: Shock requiring volume or inotropes

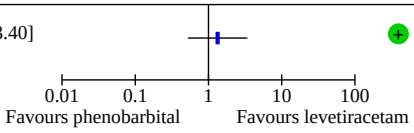
Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Risk Ratio M-H, Fixed, 99% CI	Risk Ratio M-H, Fixed, 99% CI	Risk of Bias A	B	C	D	E	F
Sharpe 2020	13	42	10	64	1.98 [0.76 , 5.15]		+	+	+	?	+	?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.9. Comparison 1: Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures, Outcome 9: Recurrence of seizure before hospital discharge

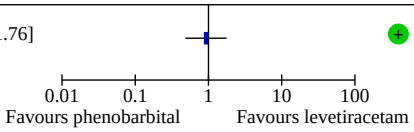
Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Sharpe 2020	7	42	8	64	1.33 [0.52 , 3.40]		+	+	+	+	+	+



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.10. Comparison 1: Phenobarbital versus levetiracetam as first-line ASM for EEG-confirmed neonatal seizures, Outcome 10: Proportion of infants with epilepsy post-discharge

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Sharpe 2020	8	18	13	27	0.92 [0.48 , 1.76]		+	+	+	+	+	+



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

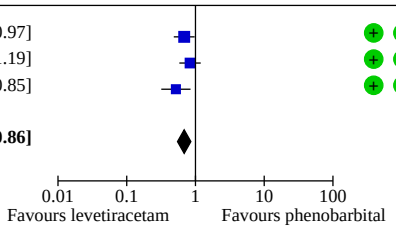
Comparison 2. Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Proportion of infants who achieve seizure control after the first loading dose of ASM	3	286	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.55, 0.86]
2.2 Proportion of infants who achieve seizure control after the maximal loading dose of ASM	3	260	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.47, 0.72]
2.3 Mortality before hospital discharge	6	452	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.82, 2.43]
2.4 Requirement for mechanical ventilation	5	394	Risk Ratio (M-H, Fixed, 95% CI)	2.20 [0.50, 9.68]
2.5 Proportion of infants who develop sedation or drowsiness	2	180	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [0.66, 5.37]
2.6 Bradycardia	4	334	Risk Ratio (M-H, Fixed, 95% CI)	6.00 [0.74, 48.97]
2.7 Hypotension requiring volume or inotropes	2	130	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.8 Shock requiring volume or inotropes	3	190	Risk Ratio (M-H, Fixed, 99% CI)	0.67 [0.30, 1.51]
2.9 Proportion of infants with an abnormal background pattern in EEG during ASM treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.10 Proportion of infants with an abnormal background pattern in EEG after stopping ASM	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.11 Duration of hospital stay	2	90	Mean Difference (IV, Fixed, 95% CI)	2.36 [0.54, 4.18]
2.12 Recurrence of seizure before hospital discharge	2	130	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.42, 6.60]
2.13 Proportion of infants with persistent seizures and/or requiring ASM at discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.14 Proportion of infants discharged on gavage feeds	2	130	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.15 Proportion of infants with an abnormal neurological examination at discharge	4	272	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.51, 1.24]
2.16 Proportion of infants who develop epilepsy post discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 1: Proportion of infants who achieve seizure control after the first loading dose of ASM

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Akeel 2022	24	52	35	52	38.1%	0.69 [0.48 , 0.97]	+ + + ? ? −
Gowda 2019	25	50	30	50	32.7%	0.83 [0.58 , 1.19]	+ + + − + −
Susnerwala 2022	13	38	29	44	29.3%	0.52 [0.32 , 0.85]	+ + + ? + ?
Total (95% CI)		**140**		**146**	**100.0%**	**0.69 [0.55 , 0.86]**	
Total events:	62		94				

Heterogeneity: Chi² = 2.39, df = 2 (P = 0.30); I² = 16%
Test for overall effect: Z = 3.32 (P = 0.0009)
Test for subgroup differences: Not applicable

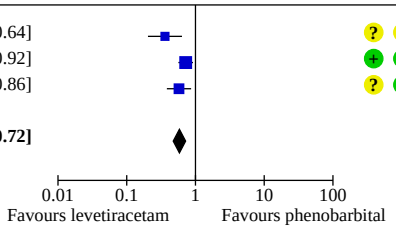


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 2: Proportion of infants who achieve seizure control after the maximal loading dose of ASM

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Ghaffar 2020	9	30	25	30	24.8%	0.36 [0.20 , 0.64]	? ? + − ? −
Gowda 2019	31	50	43	50	42.6%	0.72 [0.56 , 0.92]	+ + + − + −
Khan 2020	19	50	33	50	32.7%	0.58 [0.38 , 0.86]	? + + − ? −
Total (95% CI)		**130**		**130**	**100.0%**	**0.58 [0.47 , 0.72]**	
Total events:	59		101				

Heterogeneity: Chi² = 5.63, df = 2 (P = 0.06); I² = 64%
Test for overall effect: Z = 5.09 (P < 0.00001)
Test for subgroup differences: Not applicable

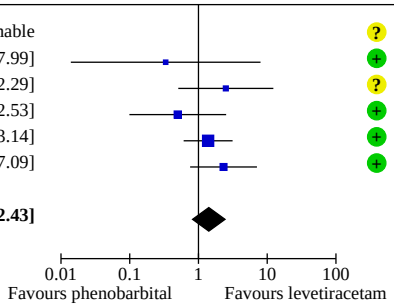


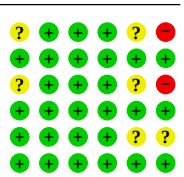
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 3: Mortality before hospital discharge

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Falsaperla 2019	0	15	0	15		Not estimable
Gowda 2019	0	50	1	50	8.0%	0.33 [0.01 , 7.99]
Khan 2020	5	50	2	50	10.6%	2.50 [0.51 , 12.29]
Perveen 2016	2	30	4	30	21.3%	0.50 [0.10 , 2.53]
Prakash 2019	10	38	8	42	40.4%	1.38 [0.61 , 3.14]
Susnerwala 2022	8	38	4	44	19.7%	2.32 [0.76 , 7.09]
Total (95% CI)		**221**		**231**	**100.0%**	**1.41 [0.82 , 2.43]**
Total events:	25		19			

Heterogeneity: Chi² = 3.62, df = 4 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable



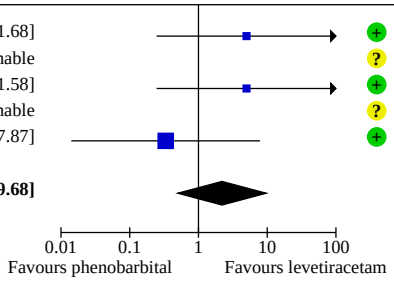


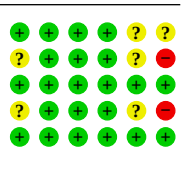
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 4: Requirement for mechanical ventilation

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akeel 2022	2	52	0	52	20.0%	5.00 [0.25 , 101.68]
Falsaperla 2019	0	15	0	15		Not estimable
Gowda 2019	2	50	0	50	20.0%	5.00 [0.25 , 101.58]
Khan 2020	0	50	0	50		Not estimable
Perveen 2016	0	30	1	30	60.0%	0.33 [0.01 , 7.87]
Total (95% CI)		**197**		**197**	**100.0%**	**2.20 [0.50 , 9.68]**
Total events:	4		1			

Heterogeneity: Chi² = 1.94, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



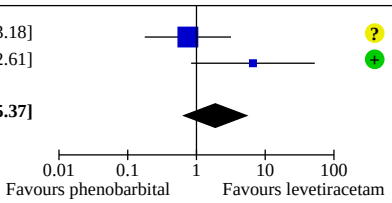


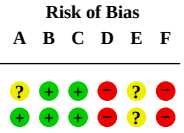
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.5. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 5: Proportion of infants who develop sedation or drowsiness

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Khan 2020	3	50	4	50	80.8%	0.75 [0.18 , 3.18]
Prakash 2019	6	38	1	42	19.2%	6.63 [0.84 , 52.61]
Total (95% CI)		**88**		**92**	**100.0%**	**1.88 [0.66 , 5.37]**
Total events:	9		5			

Heterogeneity: Chi² = 2.98, df = 1 (P = 0.08); I² = 66%
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable



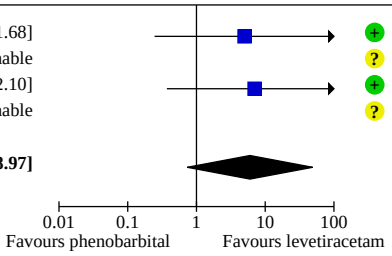


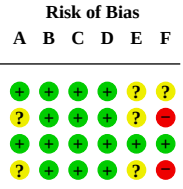
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.6. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 6: Bradycardia

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akeel 2022	2	52	0	52	50.0%	5.00 [0.25 , 101.68]
Falsaperla 2019	0	15	0	15		Not estimable
Gowda 2019	3	50	0	50	50.0%	7.00 [0.37 , 132.10]
Khan 2020	0	50	0	50		Not estimable
Total (95% CI)		**167**		**167**	**100.0%**	**6.00 [0.74 , 48.97]**
Total events:	5		0			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)
Test for subgroup differences: Not applicable



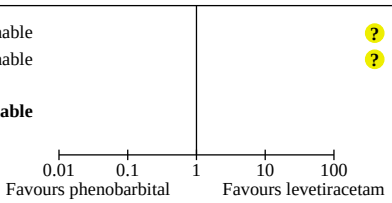


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.7. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 7: Hypotension requiring volume or inotropes

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Falsaperla 2019	0	15	0	15		Not estimable	? + + + ? −
Khan 2020	0	50	0	50		Not estimable	? + + + ? −
Total (95% CI)		**65**		**65**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

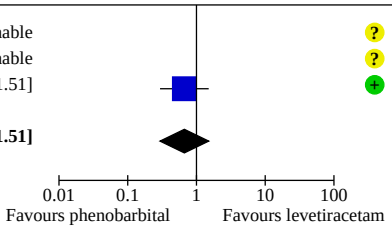


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.8. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 8: Shock requiring volume or inotropes

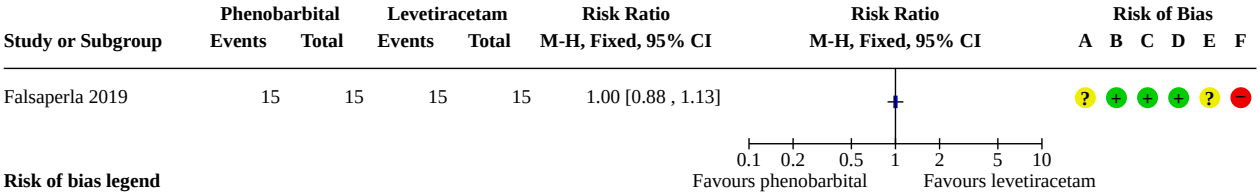
Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Weight	Risk Ratio M-H, Fixed, 99% CI	Risk of Bias A B C D E F
Falsaperla 2019	0	15	0	15		Not estimable	? + + ? ? −
Khan 2020	0	50	0	50		Not estimable	? + + ? ? −
Perveen 2016	10	30	15	30	100.0%	0.67 [0.30 , 1.51]	+ + + ? + ?
Total (99% CI)		**95**		**95**	**100.0%**	**0.67 [0.30 , 1.51]**	
Total events:	10		15				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

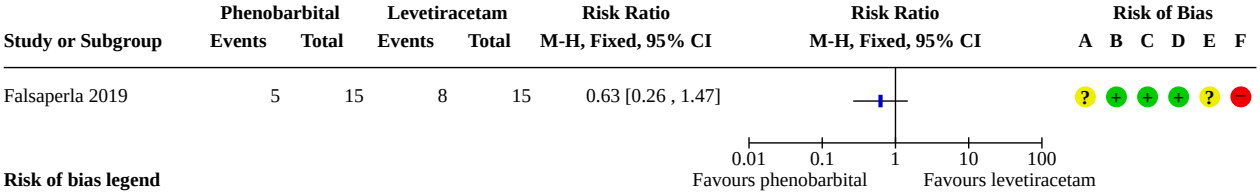
Analysis 2.9. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 9: Proportion of infants with an abnormal background pattern in EEG during ASM treatment



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

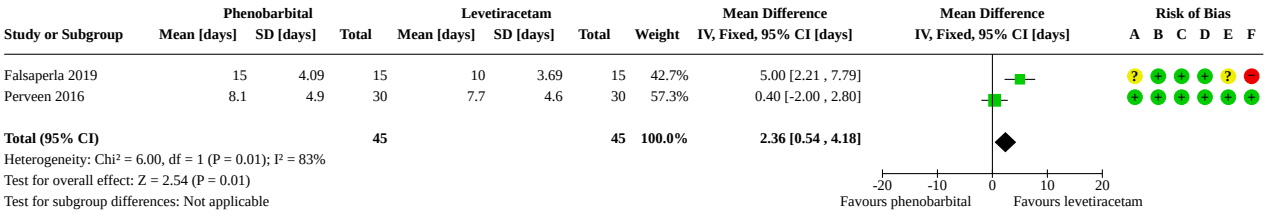
Analysis 2.10. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 10: Proportion of infants with an abnormal background pattern in EEG after stopping ASM



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.11. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 11: Duration of hospital stay



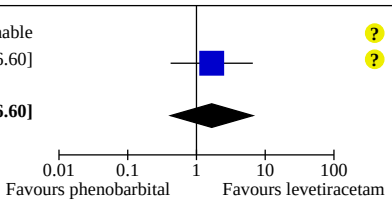
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.12. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 12: Recurrence of seizure before hospital discharge

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Falsaperla 2019	0	15	0	15		Not estimable
Khan 2020	5	50	3	50	100.0%	1.67 [0.42 , 6.60]
Total (95% CI)		**65**		**65**	**100.0%**	**1.67 [0.42 , 6.60]**
Total events:	5		3			

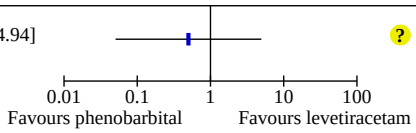
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.13. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 13: Proportion of infants with persistent seizures and/or requiring ASM at discharge

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Risk Ratio M-H, Fixed, 95% CI
Falsaperla 2019	1	15	2	15	0.50 [0.05 , 4.94]

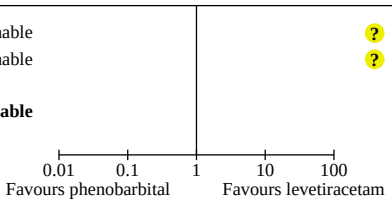


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.14. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 14: Proportion of infants discharged on gavage feeds

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Falsaperla 2019	0	15	0	15		Not estimable	? + + + ? −
Khan 2020	0	50	0	50		Not estimable	? + + + ? −
Total (95% CI)		**65**		**65**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

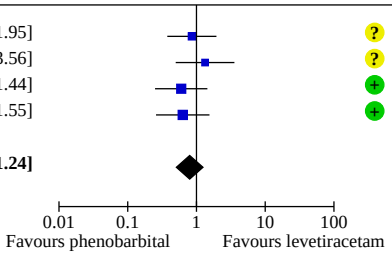


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.15. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 15: Proportion of infants with an abnormal neurological examination at discharge

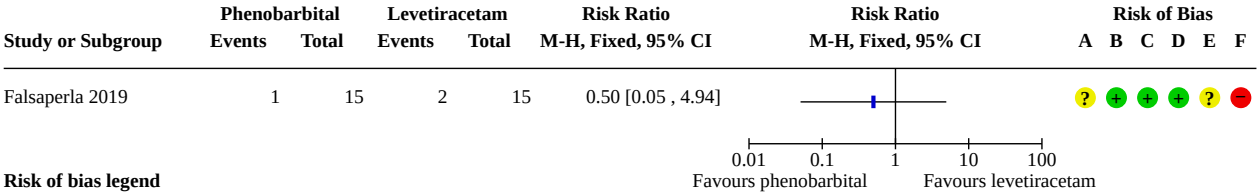
Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Levetiracetam Events	Levetiracetam Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Falsaperla 2019	6	15	7	15	21.1%	0.86 [0.38 , 1.95]	? + + ? ? −
Khan 2020	8	50	6	50	18.1%	1.33 [0.50 , 3.56]	? + + ? ? −
Perveen 2016	6	30	10	30	30.1%	0.60 [0.25 , 1.44]	+ + + ? + ?
Susnerwala 2022	6	38	11	44	30.7%	0.63 [0.26 , 1.55]	+ + + − + −
Total (95% CI)		**133**		**139**	**100.0%**	**0.80 [0.51 , 1.24]**	
Total events:	26		34				

Heterogeneity: Chi² = 1.74, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.16. Comparison 2: Phenobarbital versus levetiracetam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 16: Proportion of infants who develop epilepsy post discharge

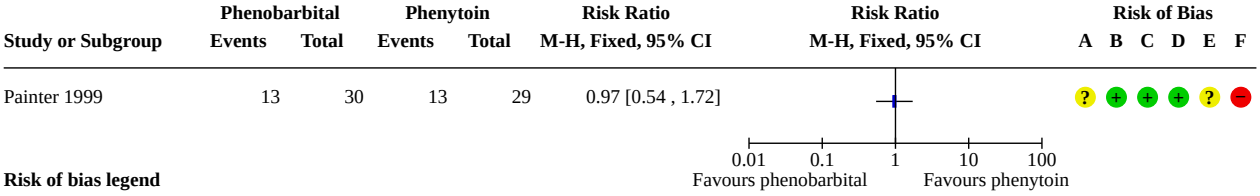


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 3. Phenobarbital versus phenytoin as first-line ASM in EEG-confirmed neonatal seizures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Proportion of infants who achieve seizure control after the maximal loading dose of ASM	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2 Arrythmias causing circulatory disturbance	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.3 Hypotension requiring volume or inotropes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.4 Bradycardia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

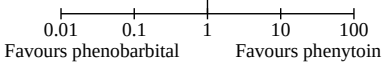
Analysis 3.1. Comparison 3: Phenobarbital versus phenytoin as first-line ASM in EEG-confirmed neonatal seizures, Outcome 1: Proportion of infants who achieve seizure control after the maximal loading dose of ASM



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.2. Comparison 3: Phenobarbital versus phenytoin as first-line ASM in EEG-confirmed neonatal seizures, Outcome 2: Arrythmias causing circulatory disturbance

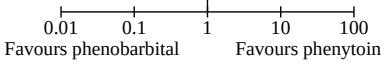
Study or Subgroup	Phenobarbital Events	Total	Phenytoin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Painter 1999	0	30	0	29	Not estimable		?	+	+	+	?	−



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.3. Comparison 3: Phenobarbital versus phenytoin as first-line ASM in EEG-confirmed neonatal seizures, Outcome 3: Hypotension requiring volume or inotropes

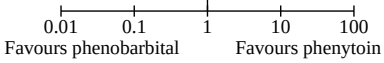
Study or Subgroup	Phenobarbital Events	Total	Phenytoin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Painter 1999	0	30	0	29	Not estimable		?	+	+	+	?	−



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.4. Comparison 3: Phenobarbital versus phenytoin as first-line ASM in EEG-confirmed neonatal seizures, Outcome 4: Bradycardia

Study or Subgroup	Phenobarbital Events	Total	Phenytoin Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Painter 1999	0	30	0	29	Not estimable		?	+	+	+	?	−

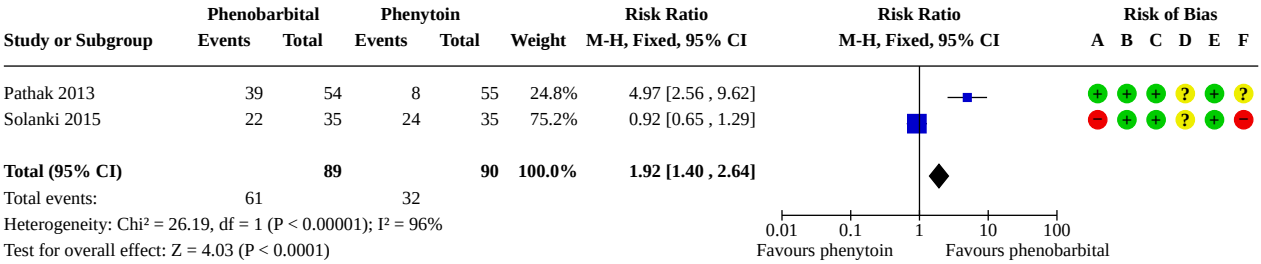


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 4. Phenobarbital versus phenytoin as first-line ASM in clinically diagnosed neonatal seizures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Proportion of infants who achieve seizure control after the first loading dose of ASM	2	179	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.40, 2.64]
4.2 Mortality before hospital discharge	2	179	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.79, 2.26]
4.3 Requirement of mechanical ventilation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.4 Proportion of infants who develop sedation or drowsiness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.5 Bradycardia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.6 Proportion of infants with persistent seizures and/or requiring ASM at discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Phenobarbital versus phenytoin as first-line ASM in clinically diagnosed neonatal seizures, Outcome 1: Proportion of infants who achieve seizure control after the first loading dose of ASM



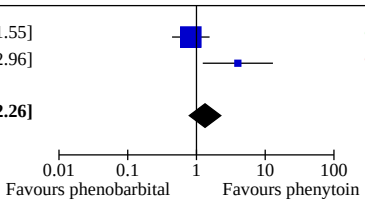
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.2. Comparison 4: Phenobarbital versus phenytoin as first-line ASM in clinically diagnosed neonatal seizures, Outcome 2: Mortality before hospital discharge

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Phenytoin Events	Phenytoin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pathak 2013	13	54	16	55	84.1%	0.83 [0.44 , 1.55]
Solanki 2015	12	35	3	35	15.9%	4.00 [1.24 , 12.96]
Total (95% CI)		**89**		**90**	**100.0%**	**1.33 [0.79 , 2.26]**
Total events:	25		19			

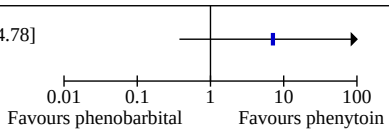
Heterogeneity: Chi² = 5.57, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 1.07 (P = 0.29)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.3. Comparison 4: Phenobarbital versus phenytoin as first-line ASM in clinically diagnosed neonatal seizures, Outcome 3: Requirement of mechanical ventilation

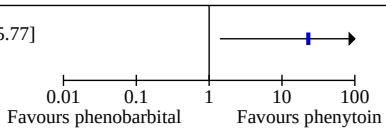
Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Phenytoin Events	Phenytoin Total	Risk Ratio M-H, Fixed, 95% CI
Pathak 2013	3	54	0	55	7.13 [0.38 , 134.78]



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

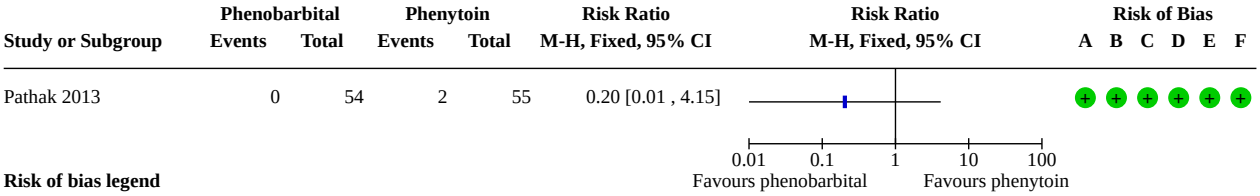
Analysis 4.4. Comparison 4: Phenobarbital versus phenytoin as first-line ASM in clinically diagnosed neonatal seizures, Outcome 4: Proportion of infants who develop sedation or drowsiness

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Phenytoin Events	Phenytoin Total	Risk Ratio M-H, Fixed, 95% CI
Solanki 2015	11	35	0	35	23.00 [1.41 , 375.77]



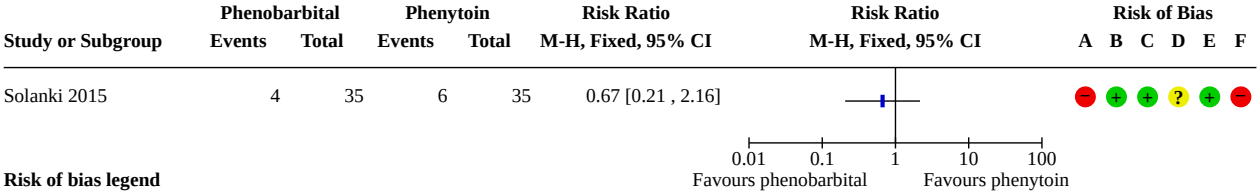
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.5. Comparison 4: Phenobarbital versus phenytoin as first-line ASM in clinically diagnosed neonatal seizures, Outcome 5: Bradycardia



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.6. Comparison 4: Phenobarbital versus phenytoin as first-line ASM in clinically diagnosed neonatal seizures, Outcome 6: Proportion of infants with persistent seizures and/or requiring ASM at discharge



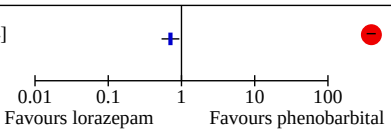
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 5. Phenobarbital versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Proportion of infants who achieve seizure control after the first loading dose of ASM	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.2 Mortality before hospital discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.3 Proportion of infants who develop sedation or drowsiness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.4 Proportion of infants with persistent seizures and/or requiring ASM at discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Phenobarbital versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 1: Proportion of infants who achieve seizure control after the first loading dose of ASM

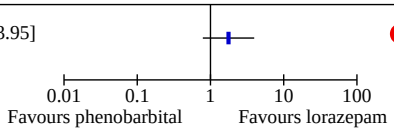
Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Lorazepam Events	Lorazepam Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Solanki 2015	22	35	32	36	0.71 [0.53 , 0.94]	−	+	+	?	+	−



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.2. Comparison 5: Phenobarbital versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 2: Mortality before hospital discharge

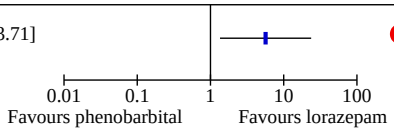
Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Lorazepam Events	Lorazepam Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Solanki 2015	12	35	7	36	1.76 [0.79 , 3.95]	−	+	+	+	+	−



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

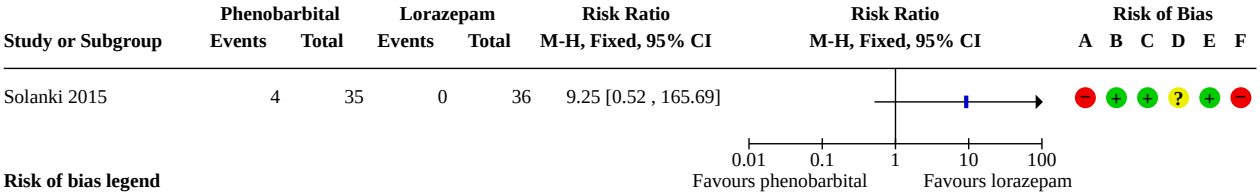
Analysis 5.3. Comparison 5: Phenobarbital versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 3: Proportion of infants who develop sedation or drowsiness

Study or Subgroup	Phenobarbital Events	Phenobarbital Total	Lorazepam Events	Lorazepam Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Solanki 2015	11	35	2	36	5.66 [1.35 , 23.71]	−	+	+	?	+	−



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.4. Comparison 5: Phenobarbital versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 4: Proportion of infants with persistent seizures and/or requiring ASM at discharge

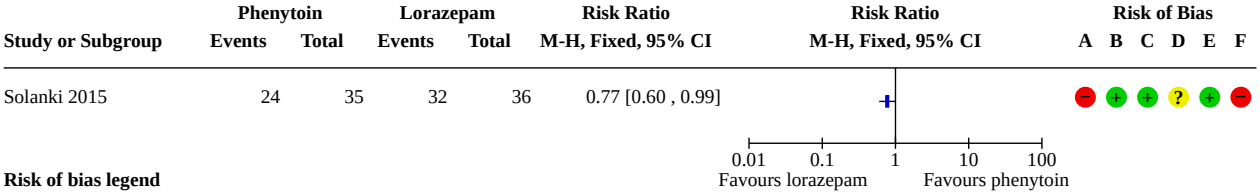


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 6. Phenytoin versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Proportion of infants who achieve seizure control after the first loading dose of ASM	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.2 Mortality before hospital discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.3 Proportion of infants who develop sedation or drowsiness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.4 Proportion of infants with persistent seizures and/or requiring ASM at discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

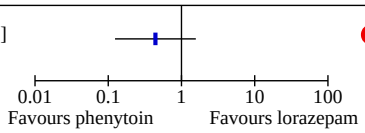
Analysis 6.1. Comparison 6: Phenytoin versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 1: Proportion of infants who achieve seizure control after the first loading dose of ASM



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.2. Comparison 6: Phenytoin versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 2: Mortality before hospital discharge

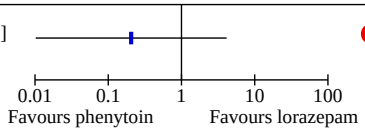
Study or Subgroup	Phenytoin Events	Phenytoin Total	Lorazepam Events	Lorazepam Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Solanki 2015	3	35	7	36	0.44 [0.12 , 1.57]		−	+	+	+	+	−



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.3. Comparison 6: Phenytoin versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 3: Proportion of infants who develop sedation or drowsiness

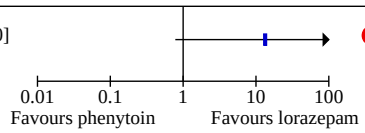
Study or Subgroup	Phenytoin Events	Phenytoin Total	Lorazepam Events	Lorazepam Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Solanki 2015	0	35	2	36	0.21 [0.01 , 4.13]		−	+	+	?	+	−



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.4. Comparison 6: Phenytoin versus lorazepam as first-line ASM in clinically diagnosed neonatal seizures, Outcome 4: Proportion of infants with persistent seizures and/or requiring ASM at discharge

Study or Subgroup	Phenytoin Events	Phenytoin Total	Lorazepam Events	Lorazepam Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Solanki 2015	6	35	0	36	13.36 [0.78 , 228.60]		−	+	+	?	+	−

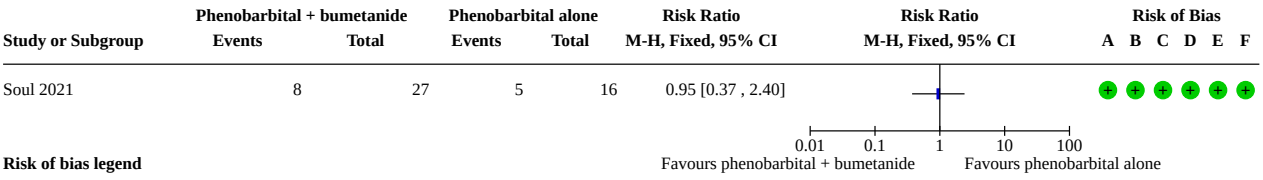


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 7. Phenobarbital + bumetanide versus phenobarbital alone as first-line ASM in EEG-confirmed neonatal seizures

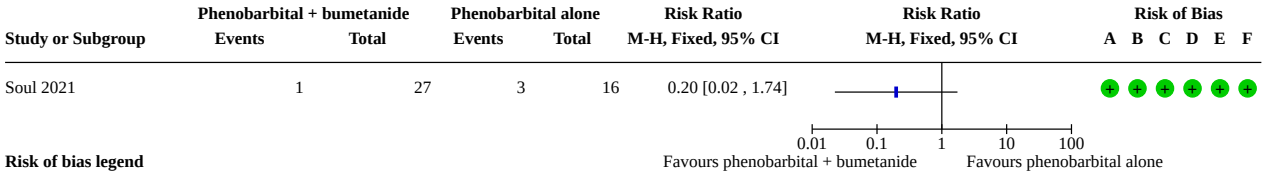
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Proportion of infants who achieve seizure control after the first loading dose of ASM	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.2 Mortality before hospital discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.3 Proportion of infants with cognitive impairment at 18-24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.4 Seizure burden during hospitalisation	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.5 Requirement for mechanical ventilation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.6 Hypotension requiring volume or inotropes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.7 Proportion of infants with an abnormal background pattern in EEG during ASM treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.8 Proportion of infants who develop epilepsy post discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7: Phenobarbital + bumetanide versus phenobarbital alone as first-line ASM in EEG-confirmed neonatal seizures, Outcome 1: Proportion of infants who achieve seizure control after the first loading dose of ASM



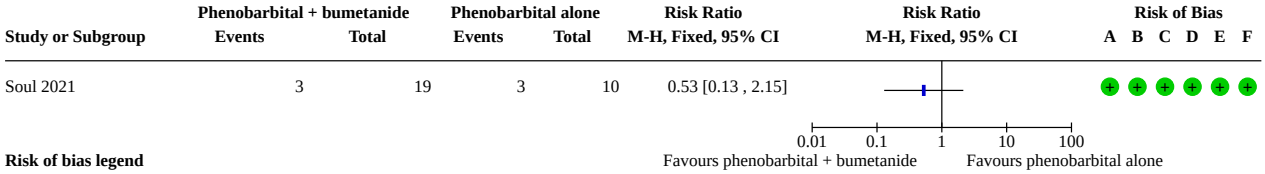
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.2. Comparison 7: Phenobarbital + bumetanide versus phenobarbital alone as first-line ASM in EEG-confirmed neonatal seizures, Outcome 2: Mortality before hospital discharge



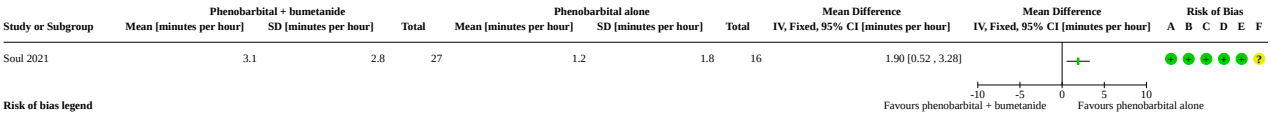
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.3. Comparison 7: Phenobarbital + bumetanide versus phenobarbital alone as first-line ASM in EEG-confirmed neonatal seizures, Outcome 3: Proportion of infants with cognitive impairment at 18-24 months



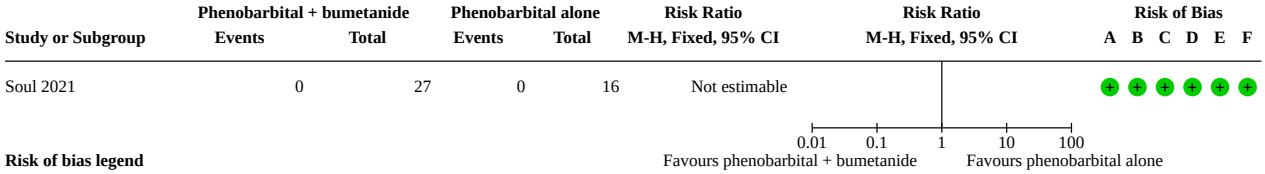
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.4. Comparison 7: Phenobarbital + bumetanide versus phenobarbital alone as first-line ASM in EEG-confirmed neonatal seizures, Outcome 4: Seizure burden during hospitalisation



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.5. Comparison 7: Phenobarbital + bumetanide versus phenobarbital alone as first-line ASM in EEG-confirmed neonatal seizures, Outcome 5: Requirement for mechanical ventilation



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

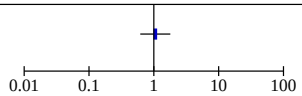
Analysis 7.6. Comparison 7: Phenobarbital + bumetanide versus phenobarbital alone as first-line ASM in EEG-confirmed neonatal seizures, Outcome 6: Hypotension requiring volume or inotropes

Study or Subgroup	Phenobarbital + bumetanide Events	Total	Phenobarbital alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Soul 2021	0	27	0	16	Not estimable		+ + + + + +

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.7. Comparison 7: Phenobarbital + bumetanide versus phenobarbital alone as first-line ASM in EEG-confirmed neonatal seizures, Outcome 7: Proportion of infants with an abnormal background pattern in EEG during ASM treatment

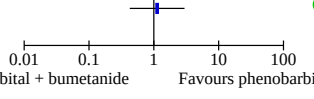
Study or Subgroup	Phenobarbital + bumetanide Events	Total	Phenobarbital alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Soul 2021	16	27	9	16	1.05 [0.62 , 1.80]		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.8. Comparison 7: Phenobarbital + bumetanide versus phenobarbital alone as first-line ASM in EEG-confirmed neonatal seizures, Outcome 8: Proportion of infants who develop epilepsy post discharge

Study or Subgroup	Phenobarbital + bumetanide Events	Total	Phenobarbital alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Soul 2021	9	26	4	13	1.13 [0.43 , 2.97]		+ + + + + +



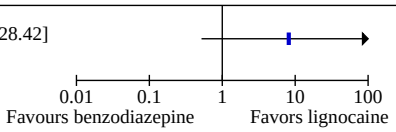
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 8. Lignocaine versus benzodiazepine as second-line ASM in EEG-confirmed neonatal seizures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Proportion of infants who achieve seizure control after the maximal loading dose of ASM	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.2 Mortality or neurodevelopmental disability at 12 months' corrected age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.3 Mortality before hospital discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.4 Neurodevelopmental disability at 12 months' corrected age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Lignocaine versus benzodiazepine as second-line ASM in EEG-confirmed neonatal seizures, Outcome 1: Proportion of infants who achieve seizure control after the maximal loading dose of ASM

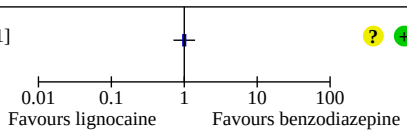
Study or Subgroup	Lignocaine Events	Lignocaine Total	Benzodiazepine Events	Benzodiazepine Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Boylan 2004	3	5	0	6	8.17 [0.52 , 128.42]		?	+	+	+	?	−



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

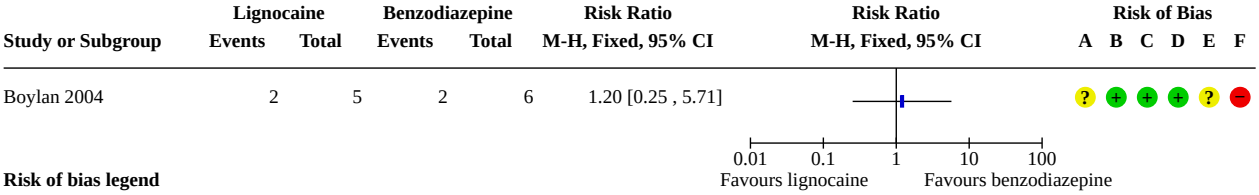
Analysis 8.2. Comparison 8: Lignocaine versus benzodiazepine as second-line ASM in EEG-confirmed neonatal seizures, Outcome 2: Mortality or neurodevelopmental disability at 12 months' corrected age

Study or Subgroup	Lignocaine Events	Lignocaine Total	Benzodiazepine Events	Benzodiazepine Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Boylan 2004	5	5	5	5	1.00 [0.71 , 1.41]		?	+	+	+	?	−



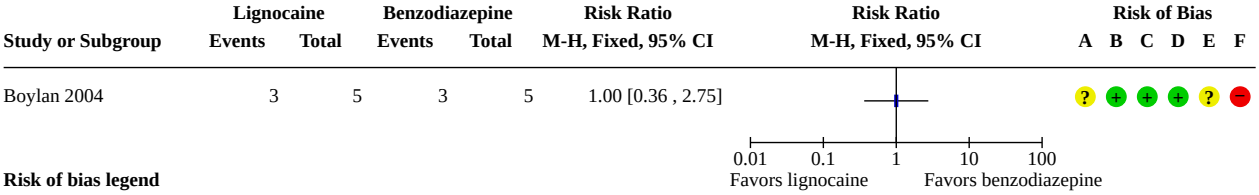
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 8.3. Comparison 8: Lignocaine versus benzodiazepine as second-line ASM in EEG-confirmed neonatal seizures, Outcome 3: Mortality before hospital discharge



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 8.4. Comparison 8: Lignocaine versus benzodiazepine as second-line ASM in EEG-confirmed neonatal seizures, Outcome 4: Neurodevelopmental disability at 12 months' corrected age



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 9. Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures

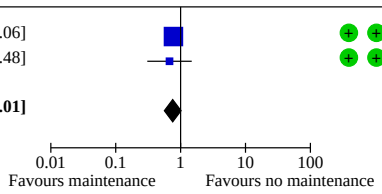
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Proportion of infants with repeat seizure before hospital discharge	2	373	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.56, 1.01]
9.2 Mortality before hospital discharge	2	373	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.39, 1.22]
9.3 Mortality at 18 to 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.4 Neurodevelopmental disability at 18 to 24 months' corrected age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.5 Requirement for mechanical ventilation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.6 Shock requiring volume or inotropes	2	373	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.67, 1.07]

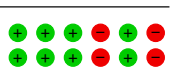
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.7 Abnormal background pattern in EEG after achieving seizure control	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.8 Duration of hospital stay	2	373	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.44, 0.70]
9.9 Proportion of infants with persistent seizures and/or requiring ASM at discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.10 Abnormal neurological examination at discharge	2	373	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.62, 1.26]
9.11 Proportion of infants who develop epilepsy post-discharge	1	126	Risk Ratio (M-H, Fixed, 95% CI)	3.18 [0.69, 14.72]

Analysis 9.1. Comparison 9: Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures, Outcome 1: Proportion of infants with repeat seizure before hospital discharge

Study or Subgroup	Maintenance ASM Events	Maintenance ASM Total	No maintenance ASM Events	No maintenance ASM Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jindal 2021	40	109	53	112	79.9%	0.78 [0.57 , 1.06]
Saxena 2016	9	77	13	75	20.1%	0.67 [0.31 , 1.48]
Total (95% CI)		**186**		**187**	**100.0%**	**0.76 [0.56 , 1.01]**
Total events:	49		66			

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.86 (P = 0.06)
Test for subgroup differences: Not applicable



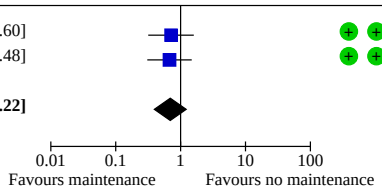


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.2. Comparison 9: Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures, Outcome 2: Mortality before hospital discharge

Study or Subgroup	Maintenance ASM Events	Maintenance ASM Total	No maintenance ASM Events	No maintenance ASM Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jindal 2021	9	109	13	112	49.3%	0.71 [0.32 , 1.60]
Saxena 2016	9	77	13	75	50.7%	0.67 [0.31 , 1.48]
Total (95% CI)		**186**		**187**	**100.0%**	**0.69 [0.39 , 1.22]**
Total events:	18		26			

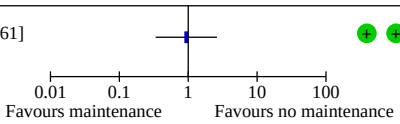
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.3. Comparison 9: Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures, Outcome 3: Mortality at 18 to 24 months

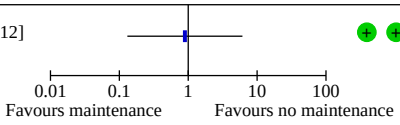
Study or Subgroup	Maintenance ASM Events	Maintenance ASM Total	No maintenance ASM Events	No maintenance ASM Total	Risk Ratio M-H, Fixed, 95% CI
Saxena 2016	6	53	7	58	0.94 [0.34 , 2.61]



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.4. Comparison 9: Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures, Outcome 4: Neurodevelopmental disability at 18 to 24 months' corrected age

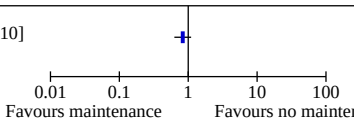
Study or Subgroup	Maintenance ASM Events	Maintenance ASM Total	No maintenance ASM Events	No maintenance ASM Total	Risk Ratio M-H, Fixed, 95% CI
Saxena 2016	2	57	2	51	0.89 [0.13 , 6.12]



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.5. Comparison 9: Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures, Outcome 5: Requirement for mechanical ventilation

Study or Subgroup	Maintenance ASM Events	Maintenance ASM Total	No maintenance ASM Events	No maintenance ASM Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Jindal 2021	47	109	58	112	0.83 [0.63 , 1.10]		+ + + + + +

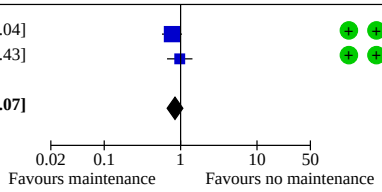


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.6. Comparison 9: Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures, Outcome 6: Shock requiring volume or inotropes

Study or Subgroup	Maintenance ASM Events	Maintenance ASM Total	No maintenance ASM Events	No maintenance ASM Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Jindal 2021	42	109	56	112	63.8%	0.77 [0.57 , 1.04]		+ + + + + +
Saxena 2016	31	77	31	75	36.2%	0.97 [0.66 , 1.43]		+ + + + + +
Total (95% CI)		**186**		**187**	**100.0%**	**0.84 [0.67 , 1.07]**		
Total events:	73		87					

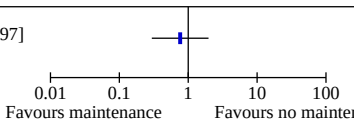
Heterogeneity: Chi² = 0.89, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.7. Comparison 9: Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures, Outcome 7: Abnormal background pattern in EEG after achieving seizure control

Study or Subgroup	Maintenance ASM Events	Maintenance ASM Total	No maintenance ASM Events	No maintenance ASM Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Saxena 2016	7	63	8	55	0.76 [0.30 , 1.97]		+ + + + + +

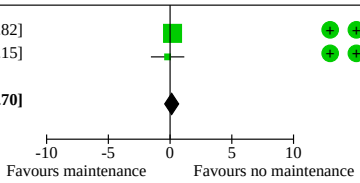


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.8. Comparison 9: Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures, Outcome 8: Duration of hospital stay

Study or Subgroup	Maintenance ASM Mean	SD	Total	No maintenance ASM Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Jindal 2021	6.5	2.1	109	6.3	2.6	112	82.5%	0.20 [-0.42 , 0.82]
Saxena 2016	7.2	4.2	77	7.4	4.3	75	17.5%	-0.20 [-1.55 , 1.15]
Total (95% CI)			**186**			**187**	**100.0%**	**0.13 [-0.44 , 0.70]**

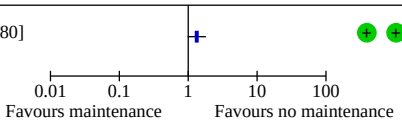
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable

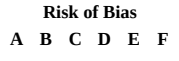


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.9. Comparison 9: Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures, Outcome 9: Proportion of infants with persistent seizures and/or requiring ASM at discharge

Study or Subgroup	Maintenance ASM Events	Total	No maintenance ASM Events	Total	Risk Ratio M-H, Fixed, 95% CI
Jindal 2021	56	112	41	109	1.33 [0.98 , 1.80]



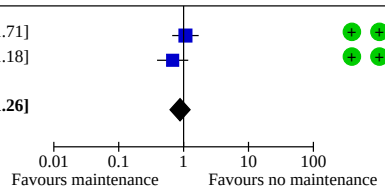


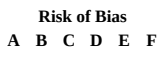
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.10. Comparison 9: Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures, Outcome 10: Abnormal neurological examination at discharge

Study or Subgroup	Maintenance ASM Events	Total	No maintenance ASM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jindal 2021	27	109	26	112	52.4%	1.07 [0.67 , 1.71]
Saxena 2016	16	77	23	75	47.6%	0.68 [0.39 , 1.18]
Total (95% CI)		**186**		**187**	**100.0%**	**0.88 [0.62 , 1.26]**
Total events:	43		49			

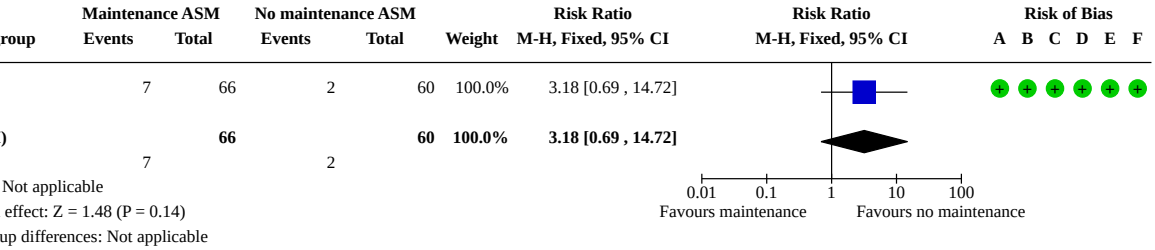
Heterogeneity: Chi² = 1.50, df = 1 (P = 0.22); I² = 34%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.11. Comparison 9: Maintenance ASM versus no maintenance ASM after achieving seizure control in clinically diagnosed neonatal seizures, Outcome 11: Proportion of infants who develop epilepsy post-discharge

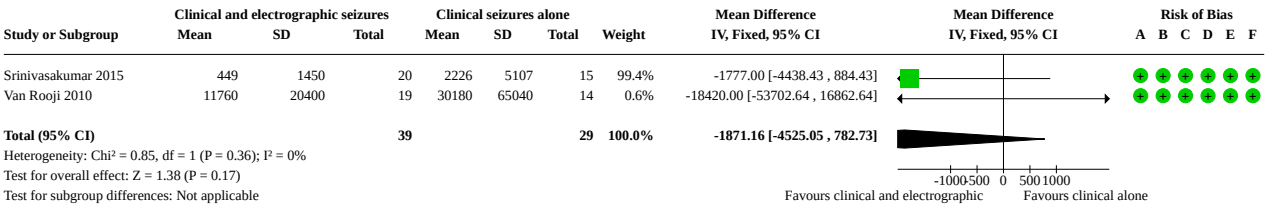


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 10. Treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Seizure burden during hospitalisation	2	68	Mean Difference (IV, Fixed, 95% CI)	-1871.16 [-4525.05, 782.73]
10.2 Mortality before hospital discharge	2	68	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.28, 1.27]
10.3 Proportion of infants who develop epilepsy post-discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10: Treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates, Outcome 1: Seizure burden during hospitalisation

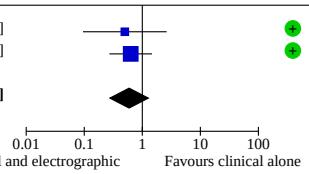


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 10.2. Comparison 10: Treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates, Outcome 2: Mortality before hospital discharge

Study or Subgroup	Clinical and electrographic seizures Events	Total	Clinical seizures alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Srinivasakumar 2015	2	20	3	15	29.8%	0.50 [0.10 , 2.63]
Van Rooji 2010	6	19	7	14	70.2%	0.63 [0.27 , 1.47]
Total (95% CI)		**39**		**29**	**100.0%**	**0.59 [0.28 , 1.27]**
Total events:	8		10			

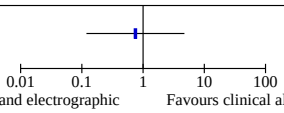
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 10.3. Comparison 10: Treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates, Outcome 3: Proportion of infants who develop epilepsy post-discharge

Study or Subgroup	Clinical and electrographic seizures Events	Total	Clinical seizures alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
Srinivasakumar 2015	2	20	2	15	0.75 [0.12 , 4.73]



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

APPENDICES

Appendix 1. May 2022 Searches

Resource	N
MEDLINE	6863 (6702 trials 161 SR)
Embase	2133 (1962 trials 171 SR)
CENTRAL	1491
Epistemonikos	76
ClincialTrials.gov	594
ICTRP	112
Other sources	3

(Continued)

Total	11,272

Database: MEDLINE (MEDALL)

Host: Ovid

Data parameters: 1946 to May 13, 2022

Date of search: 16 May 2022

#	Searches	Results
1	exp infant, newborn/ or Intensive Care, Neonatal/ or Intensive Care Units, Neonatal/ or Gestational Age/	702970
2	(babe or babes or baby* or babies or gestational age? or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born? or newly born or premature or pre-mature or pre-matures or prematures or prematurity or pre-maturity or preterm or preterms or pre term? or preemie or preemies or premies or premie or VLBW or VLBWI or VLBW-I or VLBWs or LBW or LBWI or LBWs or ELBW or ELBWI or ELBWs or NICU or NICUs).ti,ab,kw,kf.	994641
3	1 or 2 [Neonatal search filter]	1303636
4	Anticonvulsants/	54692
5	*Seizures/	36682
6	(anticonvuls* or anti-convuls* or antiepileptic* or anti-epileptic* or anti-seizur*or anti-seizur* or (seizur* adj2 prevent*) or seizur*).ti,ab,kw,kf.	164674
7	4 or 5 or 6 [terms for seizure]	190968
8	randomized controlled trial.pt.	568423
9	controlled clinical trial.pt.	94868
10	randomized.ti,ab.	608631
11	placebo.ti,ab.	234348
12	drug therapy.fs.	2490206
13	randomly.ti,ab.	383116
14	trial.ti,ab.	696888
15	groups.ti,ab.	2378348
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 [Cochrane HSSS]	5417493
17	(quasirandom* or quasi-random* or randomi* or randomly).ti,ab,kw,kf.	1040889

(Continued)

18	(control* adj2 (group? or random* or trial? or study)).ti,ab,kw,kf.	1036086
19	17 or 18 [additional trials terms]	1611025
20	16 or 19 [combining HSSS or additional terms]	5695751
21	meta-analysis/ or "systematic review"/ or network meta-analysis/	273123
22	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.	268897
23	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.	34361
24	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.	35120
25	(hand search* or handsearch*).ti,ab,kf,kw.	10457
26	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.	31953
27	meta-analysis as topic/ or network meta-analysis/	24965
28	(meta analy* or metanaly* or meta regression* or metaregression*).ti,ab,kf,kw.	236014
29	(medline or cochrane or pubmed or medlars or embase or cinahl).ab.	288285
30	(cochrane or systematic review?).jw.	19174
31	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 [CADTH SR filter]	547208
32	(2020* or 2021* or 2022*).dt,dp,ed,ep,yr.	4376776
33	31 and 32	182970
34	3 and 7 and 20 [Neonates AND Seizures AND RCT filter]	6702
35	3 and 7 and 33 [Neonates AND Seizures AND SRs date limited 2020-current]	161

Database: Embase

Host: Ovid

Data parameters: 1980 to 2022 Week 19

Date of search: 16 May 2022

#	Searches	Results
1	newborn/ or prematurity/ or newborn intensive care/ or newborn care/ or gestational age/	701545

(Continued)

2	(babe or babes or baby* or babies or gestational age? or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born? or newly born or premature or pre-mature or pre-matures or prematures or prematurity or pre-maturity or preterm or preterms or pre term? or preemie or preemies or premies or premie or VLBW or VLBWI or VLBW-I or VLBWs or LBW or LBWI or LBWs or ELBW or ELBWI or ELBWs or NICU or NICUs).ti,ab,kw,kf.	1116223
3	1 or 2 [neonates filter]	1353539
4	*anticonvulsive agent/	23296
5	*seizure/	40709
6	(anticonvuls* or anti-convuls* or antiepileptic* or anti-epileptic* or anti-seizur*or anti-seizur* or (seizur* adj2 prevent*) or seizur*).ti,ab,kw,kf.	238735
7	4 or 5 or 6 [terms for seizure]	247955
8	Randomized controlled trial/ or Controlled clinical study/	893379
9	random$.ti,ab,kw.	1776894
10	Randomization/	93533
11	placebo.ti,ab,kw.	334789
12	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,kw.	248705
13	double blind procedure/	191703
14	(controlled adj7 (study or design or trial)).ti,ab,kw.	402960
15	parallel group$1.ti,ab.	29261
16	(crossover or cross over).ti,ab.	113486
17	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	375586
18	(open adj label).ti,ab.	96587
19	(quasirandom* or quasi-random* or randomi* or randomly).ti,ab,kw,kf.	1454219
20	(control* adj2 (group? or random*)).ti,ab,kw,kf.	1177241
21	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 [trials filter]	3030443
22	meta-analysis/ or "systematic review"/ or "meta analysis (topic)"/	498280
23	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kw.	326015
24	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kw.	48224

(Continued)

25	(data synthes* or data extraction* or data abstraction*).ti,ab,kw.	42804
26	(hand search* or handsearch*).ti,ab,kw.	12732
27	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kw.	42052
28	(meta analy* or metanaly* or meta regression* or metaregression*).ti,ab,kw.	301073
29	(medline or cochrane or pubmed or medlars or embase or cinahl).ab.	362905
30	(cochrane or systematic review?).jn,jx.	30615
31	(overview adj2 reviews).ti.	108
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	776900
33	(2020* or 2021* or 2022*).yr.	4242025
34	32 and 33 [CADTH SR filter limited to the last 2 years]	200764
35	3 and 7 and 34 [results of the SR search]	171
36	3 and 7 and 21[results of the search for trials]	1962

Database: Cochrane CENTRAL

Host: Wiley interface

Data parameters: Issue 5 of 12, May 2022

Date of search: 16 May 2022

ID Search Hits

#1 MeSH descriptor: [Infant, Newborn] explode all trees 17416

#2 MeSH descriptor: [Intensive Care, Neonatal] this term only 353

#3 MeSH descriptor: [Intensive Care Units, Neonatal] this term only 853

#4 MeSH descriptor: [Gestational Age] this term only 2760

#5 ("babe" or "babes" or baby* or "babies" or "gestational age?" or infant? or "infantile" or infancy or "low birth weight?" or "low birthweight?" or neonat* or "neo-nat*" or newborn* or "new born?" or "newly born" or "premature" or "pre-mature" or "pre-matures" or prematures or prematurity or "pre-maturity" or "preterm" or "preterms" or "pre term?" or "preemie" or "preemies" or "premies" or "premie" or "VLBW" or "VLBWI" or "VLBW-I" or "VLBWs" or "LBW" or "LBWI" or "LBWs" or "ELBW" or "ELBWI" or "ELBWs" or "NICU" or "NICUs"):ti,ab,kw 96816

#6 #1 OR #2 OR #3 OR #4 OR #5 96816

#7 MeSH descriptor: [Anticonvulsants] this term only 2535

#8 MeSH descriptor: [Seizures] this term only 1035

#9 (anticonvuls* or anti-convuls* or antiepileptic* or anti-epileptic* or antiseizur*or anti-seizur* or (seizur* NEAR/2 prevent*) or seizur*):ti,ab,kw 12276

#10 #7 or #8 or #9 12276

#11 #6 AND #10 1570

Database: Epistemonikos

Host: https://www.epistemonikos.org/en/

Date of search: 16 May 2022

((babe OR babes OR baby OR babies OR "gestational age" OR "gestational ages" OR infant OR infants OR infantile OR infancy OR "low birth weight" OR "low birthweight" OR neonate OR neonatal OR "neo nate" OR "neo natal" OR newbORn OR "new bORn" OR newborns OR "new borns" OR "newly bORn" OR premature OR "pre mature" OR "pre matures" OR prematures OR prematurity OR "pre maturity" OR preterm OR preterms OR "pre term" OR preemie OR preemies OR premies OR premie OR VLBW OR VLBWI OR "VLBW I" OR VLBWs OR LBW OR LBWI OR LBWs OR ELBW OR ELBWI OR ELBWs OR NICU OR NICUs) AND (anticonvulsant OR anticonvulsants OR "anti convulsant" OR "anti convulsants" OR antiepileptic OR antiepileptics OR "anti epileptic" OR antiseizure OR antiseizures OR "anti-seizure" OR "anti seizures" OR seizure))

Resource: ClinicalTrials.gov

Host: https://clinicaltrials.gov/

Date of search: 12 April 2022

Searcher location: London, UK.

The search was run in expert search using the following search string. The results were downloaded and imported into EndNote.

((babe OR babes OR baby OR babies OR "gestational age" OR "gestational ages" OR infant OR infants OR infantile OR infancy OR "low birth weight" OR "low birthweight" OR neonate OR neonatal OR "neo nate" OR "neo natal" OR newbORn OR "new bORn" OR newborns OR "new borns" OR "newly bORn" OR premature OR "pre mature" OR "pre matures" OR prematures OR prematurity OR "pre maturity" OR preterm OR preterms OR "pre term" OR preemie OR preemies OR premies OR premie OR VLBW OR VLBWI OR "VLBW I" OR VLBWs OR LBW OR LBWI OR LBWs OR ELBW OR ELBWI OR ELBWs OR NICU OR NICUs) AND (anticonvulsant OR anticonvulsants OR "anti convulsant" OR "anti convulsants" OR antiepileptic OR antiepileptics OR "anti epileptic" OR antiseizure OR antiseizures OR "anti-seizure" OR "anti seizures" OR seizure))

Resource: ICTRP

Host: https://trialsearch.who.int/

Date of search: 16 May 2022

Searcher location: London, UK.

The following search strings were run separately in the basic search box.

((babe OR babes OR baby OR babies OR "gestational age" OR "gestational ages" OR infant OR infants OR infantile OR infancy OR "low birth weight" OR "low birthweight" OR neonate OR neonatal OR "neo nate" OR "neo natal" OR newbORn OR "new bORn" OR newborns OR "new borns" OR "newly bORn" OR premature OR "pre mature" OR "pre matures" OR prematures OR prematurity OR "pre maturity" OR preterm OR preterms OR "pre term" OR preemie OR preemies OR premies OR premie OR VLBW OR VLBWI OR "VLBW I" OR VLBWs OR LBW OR LBWI OR LBWs OR ELBW OR ELBWI OR ELBWs OR NICU OR NICUs) AND (anticonvulsant OR anticonvulsants OR "anti convulsant" OR "anti convulsants" OR antiepileptic OR antiepileptics OR "anti epileptic" OR antiseizure OR antiseizures OR "anti-seizure" OR "anti seizures" OR seizure))

Appendix 2. June 2023 Searches

Resource	N
CENTRAL	112
MEDLINE	603 (515 Trials 88 SR)
Embase	283 (158 Trials 125 SR)
Epistemonikos	0

(Continued)

ClincialTrials.gov	655
ICTRP	80
Total	1737

Database: Cochrane CENTRAL

Host: Wiley interface

Data parameters: Issue 6 of 12, June 2023

Date of search: 7 June 2023

ID Search Hits

#1 MeSH descriptor: [Infant, Newborn] explode all trees 20484

#2 MeSH descriptor: [Intensive Care, Neonatal] this term only 375

#3 MeSH descriptor: [Intensive Care Units, Neonatal] this term only 1025

#4 MeSH descriptor: [Gestational Age] this term only 3956

#5 ("babe" or "babes" or baby* or "babies" or "gestational age?" or infant? or "infantile" or infancy or "low birth weight?" or "low birthweight?" or neonat* or "neo-nat*" or newborn* or "new born?" or "newly born" or "premature" or "pre-mature" or "pre-matures" or prematures or prematurity or "pre-maturity" or "preterm" or "preterms" or "pre term?" or "preemie" or "preemies" or "premies" or "premie" or "VLBW" or "VLBWI" or "VLBW-I" or "VLBWs" or "LBW" or "LBWI" or "LBWs" or "ELBW" or "ELBWI" or "ELBWs" or "NICU" or "NICUs"):ti,ab,kw 105658

#6 #1 OR #2 OR #3 OR #4 OR #5 105658

#7 MeSH descriptor: [Anticonvulsants] this term only 2972

#8 MeSH descriptor: [Seizures] this term only 1269

#9 (anticonvuls* or anti-convuls* or antiepileptic* or anti-epileptic* or antiseizur*or anti-seizur* or (seizur* NEAR/2 prevent*) or seizur*):ti,ab,kw 13195

#10 #7 or #8 or #9 13195

#11 #6 AND #10 1720

Database: MEDLINE (MEDALL)

Host: Ovid

Data parameters: 1946 to June 06, 2023

Date of search: 7 June 2023

#	Searches	Results
1	exp infant, newborn/ or Intensive Care, Neonatal/ or Intensive Care Units, Neonatal/ or Gestational Age/	721745
2	(babe or babes or baby* or babies or gestational age? or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born? or newly born or premature or pre-mature or pre-matures or prematures or prematurity or pre-maturity or preterm or preterms or	1040979

(Continued)

	pre term? or preemie or preemies or premies or premie or VLBW or VLBWI or VLBW-I or VLBWs or LBW or LBWI or LBWs or ELBW or ELBWI or ELBWs or NICU or NICUs).ti,ab,kw,kf.	
3	1 or 2	1352125
4	Anticonvulsants/	55873
5	*Seizures/	36947
6	(anticonvuls* or anti-convuls* or antiepileptic* or anti-epileptic* or anti-seizur*or anti-seizur* or (seizur* adj2 prevent*) or seizur*).ti,ab,kw,kf.	173161
7	4 or 5 or 6	199675
8	randomized controlled trial.pt.	594019
9	controlled clinical trial.pt.	95326
10	randomized.ti,ab.	658117
11	placebo.ti,ab.	245248
12	drug therapy.fs.	2596416
13	randomly.ti,ab.	410650
14	trial.ti,ab.	754362
15	groups.ti,ab.	2553341
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	5741348
17	(quasirandom* or quasi-random* or randomi* or randomly).ti,ab,kw,kf.	1121180
18	(control* adj2 (group? or random* or trial? or study)).ti,ab,kw,kf.	1118054
19	17 or 18	1729481
20	16 or 19	6040695
21	meta-analysis/ or "systematic review"/ or network meta-analysis/	313819
22	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.	317658
23	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.	38620
24	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.	40155
25	(hand search* or handsearch*).ti,ab,kf,kw.	11100
26	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.	35453
27	meta-analysis as topic/ or network meta-analysis/	27037

(Continued)

28	(meta analy* or metanaly* or meta regression* or metaregression*).ti,ab,k-f,kw.	273051
29	(medline or cochrane or pubmed or medlars or embase or cinahl).ab.	332990
30	(cochrane or systematic review?).jw.	20267
31	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	622595
32	(2022* or 2023*).dt,dp,ed,ep,yr.	2737024
33	3 and 7 and 20 and 32	515
34	3 and 7 and 31 and 32	88

Database: Embase

Host: Ovid

Data parameters: 1980 to 2023 Week 22

Date of search: 7 June 2023

#	Searches	Results
1	newborn/ or prematurity/ or newborn intensive care/ or newborn care/ or gestational age/	750499
2	(babe or babes or baby* or babies or gestational age? or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born? or newly born or premature or pre-mature or pre-matures or prematures or prematurity or pre-maturity or preterm or preterms or pre term? or preemie or preemies or premies or premie or VLBW or VLBWI or VLBW-I or VLBWs or LBW or LBWI or LBWs or ELBW or ELBWI or ELBWs or NICU or NICUs).ti,ab,kw,kf.	1202220
3	1 or 2	1450047
4	*anticonvulsive agent/	24042
5	*seizure/	43417
6	(anticonvuls* or anti-convuls* or antiepileptic* or anti-epileptic* or anti-seizur*or anti-seizur* or (seizur* adj2 prevent*) or seizur*).ti,ab,kw,kf.	256824
7	4 or 5 or 6	266149
8	Randomized controlled trial/ or Controlled clinical study/	975168
9	random$.ti,ab,kw.	1961250
10	Randomization/	99003
11	placebo.ti,ab,kw.	360803

(Continued)

12	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,kw.	267132
13	double blind procedure/	207714
14	(controlled adj7 (study or design or trial)).ti,ab,kw.	447636
15	parallel group$1.ti,ab.	32220
16	(crossover or cross over).ti,ab.	121838
17	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	411882
18	(open adj label).ti,ab.	109069
19	(quasirandom* or quasi-random* or randomi* or randomly).ti,ab,kw,kf.	1601646
20	(control* adj2 (group? or random*)).ti,ab,kw,kf.	1301207
21	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	3304495
22	meta-analysis/ or "systematic review"/ or "meta analysis (topic)"/	608593
23	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kw.	399835
24	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kw.	55865
25	(data synthes* or data extraction* or data abstraction*).ti,ab,kw.	50885
26	(hand search* or handsearch*).ti,ab,kw.	13742
27	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kw.	47676
28	(meta analy* or metanaly* or meta regression* or metaregression*).ti,ab,kw.	360236
29	(medline or cochrane or pubmed or medlars or embase or cinahl).ab.	434934
30	(cochrane or systematic review?).jn,jx.	32153
31	(overview adj2 reviews).ti.	142
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	911864
33	(2022* or 2023*).yr.	2708204
34	3 and 7 and 21 and 33	158
35	3 and 7 and 32 and 33	125

Database: Epistemonikos

Host: https://www.epistemonikos.org/en/

Date of search: 7 June 2023

((babe OR babes OR baby OR babies OR "gestational age" OR "gestational ages" OR infant OR infants OR infantile OR infancy OR "low birth weight" OR "low birthweight" OR neonate OR neonatal OR "neo nate" OR "neo natal" OR newbORn OR "new bORn" OR newborns OR "new borns" OR "newly bORn" OR premature OR "pre mature" OR "pre matures" OR prematures OR prematurity OR "pre maturity" OR preterm OR preterms OR "pre term" OR preemie OR preemies OR premies OR premie OR VLBW OR VLBWI OR "VLBW I" OR VLBWs OR LBW OR LBWI OR LBWs OR ELBW OR ELBWI OR ELBWs OR NICU OR NICUs) AND (anticonvulsant OR anticonvulsants OR "anti convulsant" OR "anti convulsants" OR antiepileptic OR antiepileptics OR "anti epileptic" OR antiseizure OR antiseizures OR "anti-seizure" OR "anti seizures" OR seizure))

Resource: ClinicalTrials.gov

Host: https://clinicaltrials.gov/

Date of search: 7 June 2023

Searcher location: London, UK.

The search was run in expert search using the following search string. The results were downloaded and imported into EndNote.

((babe OR babes OR baby OR babies OR "gestational age" OR "gestational ages" OR infant OR infants OR infantile OR infancy OR "low birth weight" OR "low birthweight" OR neonate OR neonatal OR "neo nate" OR "neo natal" OR newbORn OR "new bORn" OR newborns OR "new borns" OR "newly bORn" OR premature OR "pre mature" OR "pre matures" OR prematures OR prematurity OR "pre maturity" OR preterm OR preterms OR "pre term" OR preemie OR preemies OR premies OR premie OR VLBW OR VLBWI OR "VLBW I" OR VLBWs OR LBW OR LBWI OR LBWs OR ELBW OR ELBWI OR ELBWs OR NICU OR NICUs) AND (anticonvulsant OR anticonvulsants OR "anti convulsant" OR "anti convulsants" OR antiepileptic OR antiepileptics OR "anti epileptic" OR antiseizure OR antiseizures OR "anti-seizure" OR "anti seizures" OR seizure))

Resource: ICTRP

Host: https://trialsearch.who.int/

Date of search: 7 June 2023

Searcher location: London, UK.

The following search strings were run separately in the basic search box.

((babe OR babes OR baby OR babies OR "gestational age" OR "gestational ages" OR infant OR infants OR infantile OR infancy OR "low birth weight" OR "low birthweight" OR neonate OR neonatal OR "neo nate" OR "neo natal" OR newbORn OR "new bORn" OR newborns OR "new borns" OR "newly bORn" OR premature OR "pre mature" OR "pre matures" OR prematures OR prematurity OR "pre maturity" OR preterm OR preterms OR "pre term" OR preemie OR preemies OR premies OR premie OR VLBW OR VLBWI OR "VLBW I" OR VLBWs OR LBW OR LBWI OR LBWs OR ELBW OR ELBWI OR ELBWs OR NICU OR NICUs) AND (anticonvulsant OR anticonvulsants OR "anti convulsant" OR "anti convulsants" OR antiepileptic OR antiepileptics OR "anti epileptic" OR antiseizure OR antiseizures OR "anti-seizure" OR "anti seizures" OR seizure))

HISTORY

Protocol first published: Issue 3, 2022

CONTRIBUTIONS OF AUTHORS

All the authors (TA, ST, VVR, HH, FB and RP) contributed to the development and drafting of the review manuscript.

The authors TA, ST, VVR and HH reviewed the results of the search, independently in pairs of two, and selected studies for inclusion. We resolved any disagreements by discussion with RP.

TA and ST independently extracted data for each study. We resolved any disagreements by discussion with HH.

VVR and RP independently assessed the risk of bias for each study using RoB 2. We resolved any disagreements by discussion with TA. For Boylan 2004, ROB TA and VVR assessed the risk of bias.

FB and TA independently assessed the certainty of the evidence for important outcomes. We resolved any disagreements by discussion with VVR.

TA will be guarantor of the review.

DECLARATIONS OF INTEREST

TA is an Associate editor with Cochrane Neonatal. However, she did not participate in the acceptance or editorial processes for this review.

ST is an Associate editor with Cochrane Neonatal. However, he did not participate in the acceptance or editorial processes for this review.

VVR declared that they have no conflict of interest.

RP reported that they have received the following: a contract payment to support a clinical trial from Union Chimique Belge; a payment to their employing institution UCL Institution for Child Health, London; a contract payment from Kephala (a company providing diagnostic expertise (EEG reporting), but which undertakes no drug development); honoraria from Natus for a lecture on EEG in neonatal epilepsy; and a payment from GW Pharmaceuticals for participation on an advisory board for a neuroprotective trial. They reported publication of opinions in the medical journal of Great Ormond Street Hospital, London, UK (review article on why we need new drugs for the treatment of epilepsy in infancy) and working as a Consultant in Clinical Neurophysiology at Great Ormond Street Hospital, London, UK (reporting neonatal EEG). RP is Chair of the neonatal task force at International League Against Epilepsy (ILAE). RP was chair of the neonatal working group of the International Neonatal Consortium (2017 to 2019). RP was also chair of the neonatal working group of the Brighton Collaboration.RP was involved in the trial included in the review Boylan 2004, funded by the UK National Lottery Community fund (investigator-led). RP did not participate in assessing risk of bias, GRADE, or extracting data for this trial (see Contributions of authors). RP's research is supported by the National Institute of Health Research (NIHR), Biomedical Research Centre at Great Ormond Street Hospital (GOSH), Cambridge Biomedical Research Centre NIHR, and the James Bradfield Memorial Grant / Evelyn Trust.

FB is affiliated to the ILAE Standards and Best Practice Council. FB is an Editor for Cochrane Epilepsy.

HH declared that they are a member of the ILAE Pediatric Commission; co-chair of the ILAE Neonatal Seizure Guideline Update group (co-chair) ICNA Board Member, and Head of the ICNA Finance Committee. HH received a USD 500 travel grant for lecture by the American Epilepsy Society (AES) in 2022. However as he was unable to attend the American Epilepsy Congress, he donated the grant to AES.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Vermont Oxford Network, USA

  Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Abiramalatha 2022).

- For the comparison of 'one ASM versus another', we reported the outcomes of each comparison (on individual ASMs) in separate analyses and SoF tables.
- The comparison 'any ASM treatment versus no ASM for clinically-diagnosed or electrographic-only seizures' was evaluated as 'treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone in neonates'.
- We included cross-over trials in this review. However, we did not analyse cross-over trials separately, because no study included washout periods.
- For the comparison 'one ASM versus another', the outcome 'proportion of infants who achieve seizure control after the first or maximal dose of ASM' was reported as two different outcomes: 'proportion of infants who achieve seizure control after the first loading dose of ASM' and 'proportion of infants who achieve seizure control after the maximal loading dose of ASM'.
- The outcome 'mortality at any time' was reported as 'mortality before hospital discharge or at any time later'.
- For the comparison 'lignocaine versus benzodiazepine as second-line ASM in EEG-confirmed neonatal seizures', long-term mortality or neurodevelopmental disability and neurodevelopmental disability alone were assessed until 12 months in the only included trial (Boylan 2004).
- For the comparison 'treatment of both clinical and electrographic seizures versus treatment of clinical seizures alone', the outcome 'proportion of infants who achieve seizure control' was reported as 'seizure burden during hospitalisation'.
- For the comparison 'maintenance ASM versus no maintenance ASM after achieving seizure control in neonates with clinically diagnosed seizures', the outcome 'proportion of infants who achieve seizure control' was reported as 'proportion of infants with repeated seizures before hospital discharge'.

- Though the time point of assessment for cognitive impairment was defined as three years or more in the protocol, the only trial (Soul 2021) that reported this outcome has reported cognitive impairment at 18 to 24 months.
- The following are the changes in the outcome 'adverse effects related to ASM treatment during hospitalisation'.
  - We added other possible adverse effects of ASMs as an outcome: proportion of infants with sedation or drowsiness, bradycardia, shock requiring volume or inotropes.
  - The adverse effect 'respiratory depression or hypoventilation requiring any form of respiratory support' was reported as 'requirement for mechanical ventilation'.
  - 'Hypotension' was reported as 'Hypotension requiring volume or inotropes'.
- As the dosage regimen of phenobarbital and levetiracetam was variable across the studies, we defined the first loading dose of ASM as 20 mg/kg for phenobarbital and 20 to 40 mg/kg for levetiracetam. The maximal loading dose of ASM was defined as 30 to 40 mg/kg for phenobarbital and 40 to 60 mg/kg for levetiracetam. We defined (post hoc) a time limit of 24 to 48 hours from the time of ASM administration to evaluate seizure control.
- In the SOF tables, for the outcome 'proportion of infants who develop adverse effects of ASM', we reported the two most relevant adverse effects: 'requirement for mechanical ventilation' and 'proportion of infants who develop sedation or drowsiness'.