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[Intervention Protocol]

Antiseizure medications for neonates with seizures

Thangaraj Abiramalatha[1], Sivam Thanigainathan[2], Viraraghavan Vadakkencherry Ramaswamy[3], Ronit Pressler[4], Francesco Brigo[5], Hans Hartmann[6]

[1]Neonatology, Kovai Medical Center and Hospital (KMCH); KMCH Institute of Health Sciences and Research, Coimbatore, India. [2]Neonatology, All India Institute of Medical Sciences, Jodhpur, India. [3]Department of Neonatology, Ankura Hospital for Women and Children, Hyderabad, India. [4]Great Ormond Street Hospital for Children, London, UK. [5]Department of Neurological and Movement Sciences. Section of Clinical Neurology, University of Verona, Verona, Italy. [6]Hannover Medical School, Hannover, Germany

Contact: Thangaraj Abiramalatha, abi_paeds@yahoo.com.

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

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 will analyse EEG-confirmed seizures and clinically-diagnosed seizures separately.
2. To assess maintenance therapy with ASM compared to no maintenance therapy after achieving seizure control. We will analyse EEG-confirmed seizures and clinically-diagnosed seizures separately.
3. To assess any ASM treatment compared to no ASM treatment for clinically-diagnosed or only-electrographic seizures.

BACKGROUND

Description of the condition

Seizure is defined as a transient occurrence of signs or symptoms, due to abnormal excessive or synchronous neuronal activity in the brain (Fisher 2005). The American Clinical Neurophysiology Society (ACNS) defines seizure 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 (Pressler 2021).

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 cotransporter 2 (KCC2) receptors, which result in high intracellular chloride concentration and depolarisation (Dzhala 2003; Dzhala 2005; Huttenlocher 1982; Khazipov 2004; Takashima 1980).

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 acute provoked (i.e. they occur due to an acute underlying cause), 10% to 20% are a manifestation of epilepsy (Shellhaas 2017).

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 (Glass 2013). Automated seizure detection using machine learning technology (Algorithm for Neonatal Seizure Recognition (ANSeR)) 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 multiple 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, are also being 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. 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). The loop diuretic bumetanide is sometimes used as an adjunct with GABAergic drugs, since it suppresses the excitatory action of GABA by reducing the intracellular chloride concentration (Khanna 2013).

Phenytoin, carbamazepine and lamotrigine cause blockage of voltage-gated sodium channels and inhibit repetitive neuronal firing. Levetiracetam acts 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 prevent clinical deterioration and to reduce brain damage and the risk of long-term neurodevelopmental impairment (Wirrell 2005; Yager 2002). However, ASMs may also be neurotoxic. 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% 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 potential benefits. Though these drugs have the advantage of not causing neuronal apoptosis, data regarding their efficacy 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 or not 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 will undertake 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 will analyse EEG-confirmed seizures and clinically-diagnosed seizures separately.
2. To assess maintenance therapy with ASM compared to no maintenance therapy after achieving seizure control. We will analyse EEG-confirmed seizures and clinically-diagnosed seizures separately.
3. To assess any ASM treatment compared to no ASM treatment for clinically-diagnosed or only-electrographic seizures.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), quasi-RCTs, and cluster-RCTs in this review. We will include studies on any class of ASMs that are known to be used in neonatal seizures.

We will exclude 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 will also exclude trials with prophylactic use of ASMs to prevent neonatal seizures or to improve neurodevelopmental outcomes.

Types of participants

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

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

Types of interventions

We will compare:

1. any ASM versus an alternative ASM in EEG-confirmed seizures (both ASMs used as first-, second- or third-line treatment);
2. any ASM versus an alternative ASM in clinically-diagnosed seizures (both used as first-, second- or third-line treatment);
3. maintenance therapy with ASM compared to no maintenance therapy in EEG-confirmed seizures;
4. maintenance therapy with ASM compared to no maintenance therapy in clinically-diagnosed seizures;
5. any ASM treatment compared to no ASM for clinically-diagnosed or only-electrographic seizures.

We will exclude ASMs used for indications other than neonatal seizures, such as neonatal hyperbilirubinaemia, sedation, or anaesthesia. We intend to analyse EEG-confirmed seizures and clinically-diagnosed seizures separately. This is because appropriate diagnosis of seizures is an essential prerequisite to test the efficacy of ASMs. Therefore, trials that have 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 cannot be excluded. Hence, we will analyse 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 a single dose or maximum dose of the given ASM

2. Mortality or neurodevelopmental disability at 18 to 24 months' corrected age. Neurodevelopmental disability will be 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)

Secondary outcomes

1. Mortality (at any time)
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 three 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. Respiratory depression and hypoventilation requiring any form of respiratory support
   b. Arrhythmias causing circulatory disturbance
   c. Hypotension requiring volume or inotropic support
   d. Hepatotoxicity resulting in discontinuation of therapy
   e. Acute kidney injury (of any stage)
   f. 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

Search methods for identification of studies

The Cochrane Neonatal Information Specialist developed a draft search strategy for OVID MEDLINE in consultation with the review authors (Appendix 1). This strategy will be peer-reviewed by an Information Specialist using the Peer Review of Electronic Search Strategies (PRESS) checklist (McGowan 2016; McGowan 2016a). The MEDLINE strategy will be translated, using appropriate syntax, for other databases. Methodological filters will be used to limit retrieval to RCTs and quasi-RCTs; and systematic reviews.

Electronic searches

The following databases will be searched without restrictions on language, publication year, publication type, or publication status:

1. Cochrane Central Register of Controlled Trials (CENTRAL);
2. Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations and Daily (1946 to present);
3. Ovid Embase (1974 to present).

Searching other resources

Trial registration records will be identified using CENTRAL. We will also conduct independent searches of the US National Library of Medicine (https://clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal).

We will identify conference abstracts using CENTRAL and Embase, and via the websites of The Eastern Society for Pediatric Research (www.easternspr.org/meeting/#archives) and Pediatric Academic Societies (www.pas-meeting.org/past-abstracts/). We will search Epistemonikos (www.epistemonikos.org) for related systematic reviews not identified by database searches. We will check the reference lists of included studies and the the reference lists of related systematic reviews to identify studies not captured in the database searches. We will search for errata or retractions for included studies published on PubMed (www.ncbi.nlm.nih.gov/pubmed).

Data collection and analysis

Selection of studies

We will include all randomised, quasi-randomised, and cluster-RCTs fulfilling our inclusion criteria. The authors (TA, ST, VVR, RP and HH) will review results of the search, independently in pairs of two. We will screen the titles and abstracts, followed by assessment of full-texts to select studies for inclusion. We will resolve any disagreements by discussion with a third review author (FB). We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

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

We will describe 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 will report such studies in the 'Characteristics of ongoing studies' table.

We will resolve any disagreements by discussion with a third review author (FB). Should any queries arise, or in cases for which additional data are required, we will contact study investigators/authors for clarification. We will replace any standard error of the mean by the corresponding standard deviation. One review author (TA) will enter final data for each study into Review Manager 5 (Review Manager 2020), which the other review author (RP) will

check. All review authors will review the protocol, analysis, and draft manuscript.

Assessment of risk of bias in included studies

The review authors HH, ST and VVR, independently in pairs of two, will assess the risk of bias of all included trials using version 2 of the Cochrane 'Risk of bias' tool (RoB 2) (Higgins 2019). We will resolve any disagreements by discussion or by consulting a third author (FB).

We will assess 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) determine the risk of bias (low risk, some concerns, or high risk). We will include relevant text alongside the judgements to provide supporting information for our decisions. We will decide the overall risk of bias for an outcome by its performance in all the domains: the overall judgement will be 'some concerns' if we assign a judgement of 'some concerns' for one domain, and 'high risk' if we assign a judgement of 'some concerns' for multiple domains or 'high risk' for one (or more) domains.

Measures of treatment effect

We will perform the statistical analyses using Review Manager 5 software (Review Manager 2020). We will summarise the data in a meta-analysis if they are sufficiently homogeneous, both clinically and statistically.

Dichotomous data

For dichotomous data we will present results using risk ratios (RRs) and risk differences (RDs) with 95% confidence intervals (CIs). We will calculate the number needed to treat for an additional beneficial outcome (NNTB), or number needed to treat for an additional harmful outcome (NNTH), with 95% CIs, if there is a statistically significant reduction (or increase) in RD. We will use the Peto odds ratio (Peto OR) and a 99% CI if the event rate is less than 1%. For individual listed adverse effects, we will use 99% CIs to allow for multiple testing.

Continuous data

For continuous data we will used the mean difference (MD) when outcomes were measured in the same way between trials. We will use the standardised mean difference (SMD) to combine trials that measured the same outcome but used different methods.

Unit of analysis issues

The unit of analysis will be the participating infant in individually randomised trials, and an infant will be considered only once in the analysis. The participating neonatal unit or section of a neonatal unit or hospital will be the unit of analysis in cluster-randomised trials. We will analyse them using an estimate of the intra-cluster correlation coefficient (ICC) derived from the trial (if possible), or from a similar trial or from a study with a similar population, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). If we use ICCs from a similar trial or from a study with a similar population, we will report this and conduct a sensitivity analysis to investigate the effect of variation in the ICC.

If we identify both cluster-randomised trials and individually randomised trials, we will only combine the results from both if there is little heterogeneity between the study designs, and the interaction between the effect of the intervention and the choice of randomisation unit is considered to be unlikely. We will acknowledge any possible heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate possible effects of the randomisation unit.

Dealing with missing data

Where data are missing, and cannot be derived as described, we will approach the analysis as follows:

1. we will contact the original study investigators to request the missing data;
2. where possible, we will impute missing SDs using the coefficient of variation (CV) or calculated from other available statistics including standard errors, CIs, t values and P values;
3. if the data are assumed to be missing at random, we will analyse the data without imputing any missing values;
4. if this cannot be assumed then we will impute the missing outcomes with replacement values, assuming all to have a poor outcome, and conduct sensitivity analyses to assess any change in the direction or magnitude of effect resulting from data imputation.

Assessment of heterogeneity

We will estimate the treatment effects of individual trials and examine heterogeneity among trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. We will interpret 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 will explore the possible causes (e.g. differences in study quality, participants, intervention regimens, or outcome assessments) if we identify substantial heterogeneity (i.e. an I^2 value greater than 50%).

Assessment of reporting biases

We will assess reporting bias by comparing the studies' stated primary outcomes and secondary outcomes with the reported outcomes. Where study protocols are available, we will compare these to the full publications to determine the likelihood of reporting bias. Studies that use the interventions in a potentially eligible infant population, but do not report on any of the primary and secondary outcomes, will be documented in the 'Characteristics of included studies' tables.

We will use funnel plots to screen for publication bias where there is a sufficient number of studies (more than 10) reporting the same

outcome. If publication bias is suggested by significant asymmetry of the funnel plot on visual assessment, we will incorporate this in our assessment of certainty of evidence.

Data synthesis

If we identify multiple studies that we consider to be sufficiently similar, we will perform meta-analysis using Review Manager 5 (Review Manager 2020). We will use a fixed-effect model to combine data where it is reasonable to assume that studies were estimating the same underlying treatment effect. If we deem meta-analysis to be inappropriate, we will analyse and interpret individual trials separately.

Subgroup analysis and investigation of heterogeneity

We will explore substantial statistical heterogeneity in the outcomes by visually inspecting the forest plots and by removing the outlying studies in the sensitivity analysis (Higgins 2020). Where statistical heterogeneity is significant, we will interpret the results of the meta-analyses accordingly; and we will downgrade the certainty of evidence in the 'Summary of findings' tables, according to the GRADE recommendations (see below).

Where data are available, we will consider conducting 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).

Sensitivity analysis

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

Summary of findings and assessment of the certainty of the evidence

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

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 the ASM;
7. proportion of infants who develop epilepsy post-discharge.

Two review authors (FB and TA) will independently assess the certainty of the evidence for each of the outcomes above. We will consider evidence from RCTs as being high-certainty, and will downgrade 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 will use GRADEpro GDT to create a 'Summary of findings' table to report the certainty of the evidence.

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.

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APPENDICES

Appendix 1. MEDLINE search strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to June 22, 2021

#	Searches	Results
1	exp Seizures/	66069
2	seizure$.ti,ab,kw,kf.	128519
3	convulsion?.ti,ab,kw,kf.	20162
4	exp Epilepsy/ or Epilepsy, Benign Neonatal/ or Spasms, Infantile/	115571
5	(epilep* or nonepilep* or non-epilep*).ti,ab,kw,kf.	148476
6	(Clonic or Tonic or Tonic-clonic or Clonic-tonic or Myoclonic).ti,ab,kw,kf.	39413
7	or/1-6 [Seizures or Epilepsy]	273159
8	exp anticonvulsants/ or gabapentin/ or levetiracetam/ or phenobarbital/ or phenytoin/ or topiramate/ or vigabatrin/	146247

(Continued)

9	exp Lidocaine/	24902
10	Midazolam/	9091
11	Bumetanide/	1925
12	(anticonvuls* or antiepileptic* or anti-convuls* or anti-epileptic* or antiseizur* or anti-seizur*).ti,ab,kw,kf.	54111
13	exp gaba agents/ or gaba agonists/ or gaba modulators/ or gaba uptake inhibitors/	160604
14	gamma-aminobutyric acid/ or baclofen/ or pregabalin/	43969
15	((gabaergic or gaba ergic or gamma-Aminobutyric Acid) adj2 agent?).ti,ab,kw,kf.	294
16	((gaba or gaba-a) adj1 (agents or agent or drug or drugs or effect? or receptor?)).ti,ab,kw,kf.	6725
17	exp Barbiturates/	53862
18	(Amobarbital or Barbital or Hexobarbital or Mephobarbital or Methohexital or Murexide or Phenobarbital or Primidone or Secobarbital or Thiobarbiturate? or Thiamylal or Thiopental).ti,ab,kw,kf.	28622
19	(PHENOBARBITAL or gardenal or hysteps or luminal or phenemal or phenobarbitone or phenylbarbital or phenylethylbarbituric acid or adonal or aephenal or agrypnal or alepsal or amylofene or andral or aparoxal or aphenylbarbit or aphenyletten or atrofen or austrominal or barbapil or barbellen or barbenyl or barbilettae or barbilixir or barbinal or barbiphen or barbiphenyl or barbivis or barbonal or barbonalett or barbophen or bardorm or bartol or bialminal or calmetten or calminal or carbronal or cardenal or cemalonal or codibarbital or coronaletta or cratecil or damoral or dezibarbitur or dormina or dormiral or dromural or ensobarb or ensodorm or epanal or epanal 2 or epidorm or epilol or episedal or epsylone or eskabarb or etilfen or euneryl or fenbital or fenemal or fenemal nm pharma or fenobarbital or fenolbarbital or fenosed or fenylettae or gardenal or gardenal sodium or gardenale or gardepanyl or glysoletten or haplopan or haplos or helional or hennoletten or hypnaletten or hypno tablinetten or hypno-tablinetten or hypnogen fragner or hypnolone or hypnotal or hypnotalon or hysteps or lefebar or leonal or leonal leo or lephebar or lepinal or lethyl or linasen or liquital or lixophen or lubergal or lubrokal or lumesettes or lumesyn or luminal or luminal sodium or luminale or luminaletas or luminalette or luminaletten or luminalettes or luminalum or lumofridetten or luphenil or luramin or menobarb or molinal or neurobarb or nirvonal or noptil or nova pheno or nova-pheno or nunol or parkotal or pharmetten or phen bar or phenaemal or phenemal or phenethylbarbital sodium or phenobal or phenobarb or phenobarbital 2 or phenobarbital i or phenobarbital sodium or phenobarbitol or phenobarbiton or phenobarbitone or phenobarbitone sodium or phenobarbitural or phenobarbyl or phenonyl or phenotal or phenoturic or phenoyl or phenyl ethyl barbituric acid or phenylethyl barbituric acid or phenylethylbarbituric acid or phenylethylmalonyl urea or phenylethylmalonylurea or phenyletten or phenyral or polcominal or promptonal or seda tablinen or sedabar or sedicat or sedizorin or sedlyn or sedofen or sedonal or sedonettes or seneval or sevenal or sodium phenobarbital or sodium phenobarbitone or sombutol mcclung or somnolens or somnoletten or somnosan or somonal or spasepilin or starifen or starilettae or stental or teolaxin or the-	67874

(Continued)

	olaxin or triabarb or tridezibarbitur or uni-feno or versomnal or wakobital or zadoletten or zadonal).ti,ab,kw,kf.	
20	(PHENYTOIN or antisacer or difenin or dihydan or dilantin or diphenylhydantoin or sodium diphenylhydantoinate or epamin or epanutin or fenitoin or hydantol or phenytoin or alepsin or aleviatin or antilepsin or antisacer or antisacer comp or cansoin or citrullamon or comital or cumatil or danten or dantoin or denyl or di hydan or di-hydan or di-phen or difetoin or differenin or difhydan or dihydan or dilantin or dilantin 125 or dilantin 125 infatabs or dilantin 125 kapseals or dilantin or dintoin or dintoina or diphantoin or diphantoine or diphantoine or diphedal or diphedan or diphenin or diphenin sodium or diphenine or diphenine sodium or diphentoin or diphenyl hydantoin or diphenylan or diphenyldantoin or diphenylhydantoin or diphenytoin or ditoin or ditomed or ekko or epanutin or epelin or epilantin or epileptin or eptal or eptoin or felantin or fenantoin or fenidantoin or fenitoin or fenytoin or fenytoine or hidanil or hidantal or hydantin or hydantinal or hydantoinal or hydantol or idantoin or lehydan or lepitoin or minetoin or neosidantoina or phenhydan or phenhydane or phenilep or phentytoin? or phenybin or phenydan or phenydantin or phenytek or phenytex or phenytoinum or phenytonium or prompt phenytoin sodium or pyoredol or sanepil or serum phenytoin or sodantoin or sodanton or solantoin or solantyl or tacosal or vasilcon or zentropil).ti,ab,kw,kf.	15181
21	(LEVETIRACETAM or elepsia or etiracetam or keppra or kopodex or matever or spritam or etiracetam).ti,ab,kw,kf.	4227
22	(TOPIRAMATE or epitomax or Topamax or acomicil or ecuram or epiramat or epitomax or epitoram or erravia or etopro or fagodol or jadix or lusitrax or maritop or oritop or piraleps or pirantal or pirepil or qudexy or qudexy or sincronil or talopam or tiramat or topaben or topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat or topiramato or topiratore or topit or toramat or torlepta or trokendi).ti,ab,kw,kf.	4863
23	(VIGABATRIN or sabril or sabrilex or gamma vinyl gaba or gamma vinyl gamma aminobutyric acid? or vigadrone).ti,ab,kw,kf.	2237
24	(GABAPENTIN or apo-gabapentin or convalis or neurontin or pms-gabapentin or dineurin or gabalept or gabaliquid geriasan or gabatin or gantin or gralise or kaptin or keneil or neurontin or neurotonin or nupentin).ti,ab,kw,kf.	6637
25	(LIDOCAINE or octocaine or xylesthesin or xylocaine or xylocitin or xyloneural or akten or alphacaine or anestacaine or anestacon or anestacone or aritmal or betacaine or cidancaina or corus 1030 or corus1030 or cuivasil spray or dalcaine or dentipatch or dequaspray or diethylaminodimethylacetanilid? hydrochloride or dolicaine or dube spray or duncaine or dynexan or ela-max or esracain or farmacaina or gesicain or glydo or gravocain or isicaine or jetokain or l-caine or lecasin or leostesin or lida mantle).ti,ab,kw,kf.	23720
26	(MIDAZOLAM or dormicum or versed or buccolam or dalam or doricum or dormonid or fortanest or fulsed or hypnoval or hypnovel or hypnoyvel or ipnovel or midacum or midafresa or midazo or midazol or miloz or nayzilam).ti,ab,kw,kf.	14827
27	(BUMETANIDE or bumedyl or bumethanide or bumex or burinex or drenural or fordiuran or miccil or budema or bumedyl or bumelex or bumet or bumetamide or bumetidine or bumex or burinax or burinex or busix or butinat or butinon or bymex or cambiex or drenural or farmadiuril or fontego or fordiuran or lixil or lunetoron or miccil or primex).ti,ab,kw,kf.	3153

(Continued)

28	Valproic Acid/	12939
29	(Valproate or Valproic Acid or Propylpentanoic Acid or Divalproex or Depakene or Convulsofin or Depakote or Dipropyl Acetate or Divalproex Sodium or Vupral or Propylisopropylacetic Acid or Ergenyl).ti,ab,kw,kf.	18641
30	exp Benzodiazepines/	66527
31	benzodiazepine?.ti,ab,kw,kf.	35811
32	(Alprazolam? or Anthramycin? or Bromazepam? or Clonazepam? or Devazepide? or Diazepam? or Nordazepam? or Flumazenil? or Flunitrazepam? or Flurazepam? or Nitrazepam? or Oxazepam? or Pirenzepine? or Prazepam? or Temazepam?).ti,ab,kw,kf.	36122
33	Lorazepam/	2932
34	(Lorazepam$ or Ativan or Orfidal or Temesta or Tolid or Donix or Duralozam or Durazolam or Idalprem or Laubeel or Lorazep or Novo-Lorazem or Novo Lorazem or Nu-Loraz or Nu Loraz or Sedicepan or Sinestron or Apo-Lorazepam or apolorazepam or Somagerol or Temesta).ti,ab,kw,kf.	3934
35	(fosphenytoin? or Phosphenytoin?).ti,ab,kw,kf,nm.	443
36	Paraldehyde/	376
37	Paraldehyde.ti,ab,kw,kf,nm.	566
38	Felbamate/	403
39	(Felbamate or Taloxa or Felbatol or Felbamyl or ADD-03055 or "ADD 03055" or ADD03055 or W-554 or "W 554" or W55).ti,ab,kw,kf,nm.	774
40	(AMPA adj2 antagonist?).ti,ab,kw,kf.	1717
41	Carbamazepine/	11344
42	(Carbamazepin? or Carbazepin? or Epitol or Finlepsin or Neurotol or Tegretol or Amizepin?).ti,ab,kw,kf.	15920
43	or/8-42 [Anticonvulsant and other Agents]	414302
44	Wthholding Treatment/	0
45	(witholding or ((withold or withheld or cessation or withdraw$) adj2 (treatment? or care))).ti,ab,kw,kf.	12427
46	maintenance.ti,ab,kw,kf.	290765
47	or/44-46 [Witholding Treatment Maintenance]	302699
48	Drug therapy/	30869
49	(((drug or drugs) adj2 therap$) or pharmacotherapy or pharmacotherapies).ti,ab,kw,kf.	121204
50	or/48-49 [Drug Therapy]	137920

(Continued)

51	or/43,47,50 [Interventions-drugs or related terms]	834787
52	exp seizures/dt	11459
53	exp Epilepsy/dt	27790
54	or/52-53 [Indication with drug therapy subheading]	36940
55	exp infant, newborn/	627789
56	(infant or infants or infant? or infantile or infancy or newborn* or new born or new borns or newly born or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or pre term or premies or low birth weight or low birthweight or VLBW or LBW or ELBW or NICU).ti,ab,kw,kf.	932513
57	or/55-56 [Filter: Neonatal Population 2021]	1208114
58	(randomized controlled trial or controlled clinical trial).pt.	624085
59	(randomized or randomised or randomly).ti,ab,kw,kf.	960234
60	placebo.ab.	219071
61	(trial or groups).ab.	2619260
62	drug therapy.fs.	2336505
63	((single or doubl* or tripl* or treb*) and (blind* or mask*)).ti,ab,kw,kf.	204303
64	Double-Blind Method/	165229
65	exp Animals/ not humans/	4849572
66	(or/58-64) not 65 [RCT filter]	4433643
67	systematic review.pt.	158351
68	(systematic adj2 review).ti.	157198
69	meta analysis/	135424
70	(meta-analysis or metaanalysis).ti,ab,kw.	179329
71	(cochrane or systematic review?).jw.	18576
72	overview of reviews.ti.	78
73	or/67-72 [SR filter]	313818
74	7 and 51 and 57 [Seizures AND Interventions AND Neonate]	6854
75	54 and 57 [Seizures drug therapy AND Neonates]	4026
76	or/74-75 [Results before Filters]	7497
77	76 and 73 [SR Results]	124

(Continued)

78	(76 and 66) not 77 [RCT Results]	4400

Appendix 2. Cochrane Neonatal standard search strategy

CENTRAL via CRS Web

1. MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET

2. infant or infants or infant's or "infant s" or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU AND CENTRAL:TARGET

3. #2 OR #1

MEDLINE via Ovid - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)

1. exp infant, newborn/

2. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or 'infant s' or infant's or infantile or infancy or neonat*).ti,ab.

3. 1 or 2

4. randomized controlled trial.pt.

5. controlled clinical trial.pt.

6. randomized.ab.

7. placebo.ab.

8. drug therapy.fs.

9. randomly.ab.

10. trial.ab.

11. groups.ab.

12. or/4-11

13. exp animals/ not humans.sh.

14. 12 not 13

15. 3 and 14

16. randomi?ed.ti,ab.

17. randomly.ti,ab.

18. trial.ti,ab.

19. groups.ti,ab.

20. ((single or doubl* or tripl* or treb*) and (blind* or mask*)).ti,ab.

21. placebo*.ti,ab.

22. 16 or 17 or 18 or 19 or 20 or 21

23. 2 and 22

24. limit 23 to yr="2018 -Current"

25. 15 or 24

CINAHL via EBSCOhost

(infant or infants or infant's or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW) AND (randomized controlled trial OR controlled clinical trial OR ≤ ed OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

CONTRIBUTIONS OF AUTHORS

All the authors contributed to the development of the protocol.

The authors TA, ST, RP, VVR and HH will review the results of the search, independently in pairs of two, and select studies for inclusion. We will resolve any disagreements by discussion with FB.

RP and TA will independently extract data for each study. We will resolve any disagreements by discussion with FB.

HH, ST and VVR, independently in pairs of two, will independently assess the risk of bias for each study using RoB 2.

FB and TA will independently assess the certainty of the evidence for primary outcomes.

TA will be guarantor of the protocol and the review.

DECLARATIONS OF INTEREST

TA declared that they have no conflict of interest.

ST declared that they have no conflict of interest.

VVR declared that they have no conflict of interest.

RP reports 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; a payment from GW Pharmaceuticals for participation on an advisory board for a neuroprotective trial. They report publication of opinions in the medical journal, Great Ormond Street Hospital, London, UK (review article on why we need new drugs for the treatment in 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. RP was involved in two studies that may be included in the review depending on agreed inclusion criteria: the NEMO trial (Pressler 2015), funded by the EU (FP7) (investigator-led), and Boylan 2004, funded by the UK National Lottery Community fund (investigator-led). If these trials are included, RP will not participate in assessing risk of bias, GRADE, or extracting data.

FB reports they have received fees for speaking, and travel support and accommodation from Lusofarmaco; personal payments.

HH declared that they have no conflict of interest.

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Internal sources

- No sources of support provided

External sources

- Vermont Oxford Network, USA

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