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Prophylactic antiseizure medication administration practices in neonates with hypoxic-ischaemic encephalopathy: a scoping review protocol

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ABSTRACT

Introduction Hypoxic-ischaemic encephalopathy (HIE) is a leading cause of neonatal mortality and long-term neurodevelopmental impairment worldwide. Neonatal seizures are common in HIE and are associated with adverse outcomes. While antiseizure medications are routinely used for treatment, their prophylactic use in the absence of clinically evident seizures remains controversial, with limited consensus and variable clinical practices. Therefore, this review will map the existing evidence concerning the utilisation of antiseizure medication for prophylaxis among neonates with HIE.

Methods and analysis The review will follow the Joanna Briggs Institute scoping review methodology and be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines. A comprehensive search will be conducted across various scientific databases, including PubMed, Embase, Scopus and Web of Science, guided by the Population, Intervention, Concept and Context framework, starting between October and November 2026. The review will consider studies on the prophylactic use of antiseizure medication among neonates with HIE. The collected search results will be organised and uploaded to Covidence, where duplicates will be removed, and titles and abstracts will be screened. Search and screening processes have not yet started.

Ethics and dissemination This will be a secondary study using already published information; therefore, ethical approval was not sought. All studies included in this review will be cited accordingly, as attributed to the publication licence. The data gathered will be summarised in a scoping review and submitted for publication in an international peer-reviewed journal. Datasets shall also be made publicly available in a data repository, such as the Open Science Framework.

STRENGTHS AND LIMITATIONS OF THE STUDY

⇒ This scoping review explores a clinically significant and underexplored area of prophylactic use of antiseizure medication among neonates with hypoxic-ischaemic encephalopathy.
⇒ The review follows an established methodological framework for scoping reviews.
⇒ Heterogeneity of the included studies may limit direct comparability.
⇒ Available evidence may be limited by small sample sizes, study designs and observed treatment effects.
⇒ Variability in access to continuous electroencephalogram monitoring and therapeutic hypothermia across settings may also affect the interpretation of findings.

INTRODUCTION

Hypoxic-ischaemic encephalopathy (HIE) is a condition among newborns arising from limited oxygen supply to the brain. It is estimated that over 1.2 million cases of HIE occur worldwide each year, with Sub-Saharan Africa accounting for the largest proportion.[1] Various scoring systems have been developed to assess the severity of HIE in newborns. The Sarnat and Sarnat staging grades HIE into three major stages, with stage I considered as mild HIE.[2] This stage occurs within 24 hours, and the neonates are usually hyperalert or irritable, with no seizures and mild tachycardia. These infants may also have a strong Moro reflex, normal or increased muscle tone and normal pupils. Stage II is defined as moderate HIE with features such as lethargy, hypotonia, seizures and constricted pupils.[2 3] Other features include hypotonia and bradycardia, and this stage may last between 2 and 14 days. The risk of neurodevelopmental impairment is higher in this stage, and babies often present with an abnormal electroencephalogram (EEG). Stage III is defined as severe HIE with features like frequent and refractory seizures, apnoeas, stupor and flaccidity. This stage is characterised by a poor prognosis and has an abnormal EEG.[3] Other scores used include the modified Sarnat classification and the Thompson score.[4] Recent advances have prioritised augmenting these scores with neuroimaging, such as amplitude-EEG and MRI, to determine the maximal extent of brain hypoxia.[2] These developments are essential for guiding clinicians, especially

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regarding the timing of antiseizure medication (ASM) administration.

Preterm infants and neonates who have experienced HIE, especially those in stage II and III, are very prone to developing seizures, which may predispose them to long-term neuropsychiatric conditions. A secondary analysis of results from two studies (*an observational study (NCT02160171) and a randomised controlled trial (NCT02431780)*) demonstrated that electrographic seizures occurred in over 50% of infants undergoing therapeutic hypothermia.[5] Further evidence has demonstrated a variable incidence of seizures between 30% and 65% among infants who have been diagnosed with HIE, especially during the cooling phase.[6–8] Across Tanzania, seizures constituted approximately 8.6% of the neurological presentations among infants who were diagnosed with HIE.[9] While ASMs are often given to neonates with clinically evident seizures linked to HIE, uncertainties still exist about the best methods for detecting and treating seizures. Current controversies include the treatment threshold for electrographic-only seizures, the duration or burden of seizures warranting intervention, the role of continuous electroencephalography versus amplitude-integrated electroencephalography monitoring and the clinical significance of electroclinical dissociation observed following therapeutic hypothermia or ASM administration. The threshold for initiating prophylactic antiseizure therapy may also vary with HIE severity, neurological examination findings, biochemical markers, perinatal risk factors and the timing of clinical assessment.[10] These uncertainties further complicate the rationale for prophylactic antiseizure therapy in infants without confirmed seizures. Additionally, there is still limited evidence concerning the seizure frequency, especially from the low- and middle-income settings among HIE infants, either before, during or after the therapeutic cooling.

Recommendations from the International League Against Epilepsy have fronted phenobarbitone as first-line treatment of neonatal seizures irrespective of the seizure aetiology.[10] Other agents, such as levetiracetam, midazolam, phenytoin and lidocaine, have been recommended as second-line ASM.[11–13] However, the reported efficacy of these agents is variable. For example, a randomised trial of 100 preterm neonates showed a higher efficacy with levetiracetam compared with phenobarbital in managing seizures.[14] Yet another trial involving 30 patients demonstrated higher efficacy of phenobarbitone compared with levetiracetam during the treatment of neonatal seizures.[15] Other trials and systematic reviews have found no significant difference in the efficacy of both agents in managing seizures among preterm neonates.[16 17] In Ethiopia, phenobarbitone controlled seizures in 73.9% of the infants diagnosed with HIE.[18] However, most of these studies have evaluated the use of phenobarbitone and other ASMs after the occurrence of seizures and not before. While controversial, emerging evidence demonstrates that phenobarbitone administration among asphyxiated babies before seizure onset can be protective against seizures among these infants.[19 20] The rationale for prophylactic ASM use in neonates with HIE remains complex and multifaceted. Proposed benefits include prevention of clinical or electrographic seizures, reduction in seizure burden, minimisation of cumulative ASM exposure, prevention of postneonatal epilepsy, improvement in neurodevelopmental outcomes and reduction in mortality.[13] However, these potential benefits must be balanced against possible harms, including unnecessary drug exposure in infants who may never develop seizures, acute adverse effects such as sedation, feeding difficulties, altered thermoregulation, respiratory compromise and potential long-term neurotoxicity. The balance between risks and benefits may differ across clinical settings and HIE severity categories.

Various animal studies have also raised concerns about the risks and limitations of using antiepileptic medications despite their efficacy and importance in managing neonatal seizures.[21–23] The toxicity profiles of ASMs may vary substantially according to drug class, dosing regimen, timing of administration and cumulative exposure. While prophylactic administration of a single dose may theoretically reduce seizure burden with limited toxicity, higher cumulative exposure may increase the risk of adverse neurodevelopmental effects. The risk of these drugs is often increased among neonates with different underlying comorbidities, such as renal and liver impairment. Further evidence has demonstrated neuronal apoptosis and neurotoxicity following these drug administrations.[21] Also, there is an increased risk of long-term synaptic plasticity, synaptogenesis and probable brain demyelination following the administration.[24] These risks have been rarely examined, especially after the administration of the antiepileptic medication among neonates with HIE. While ASMs are widely used for the treatment of neonatal seizures, the risks, roles and use of prophylactic ASM administration remain unclear, especially in low- and middle-income countries.[21 25] Therefore, we propose a scoping review to map and synthesise existing evidence on the use of prophylactic ASM in neonates with HIE. This review will also collect information, including indications for ASM, medication types, timing of medication administration, HIE grading, reported outcomes and any presumed risks following medication administration.

METHODS

This scoping review will follow the Joanna Briggs Institute (JBI) methodology.[26] The review will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR). The population-intervention-concept-context framework will guide the development of eligibility criteria. The population will include asphyxiated term and preterm

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infants diagnosed with HIE. HIE severity levels will be considered for subgroup analysis based on the data obtained. The intervention will include ASM to explore prophylactic administration. Context will include the different healthcare settings, such as the neonatal intensive care unit, and the studies will span low- and middle-income countries as described in the eligibility criteria.

Primary research question

What evidence exists on the use of prophylactic ASMs in neonates with HIE?

Secondary research questions

1. What prophylactic ASM regimens, including drug type, dosing strategies, timing and duration, have been studied in neonates with HIE?
2. What are the indications for prophylactic administration among neonates with HIE?
3. What outcomes are reported (eg, seizure incidence, mortality and neurodevelopment)?
4. What are the differences in practices across settings (HIC vs LMIC, among infants treated with or not treated with therapeutic hypothermia)?
5. What are the reported risks or adverse effects concerning the use of ASM for prophylaxis among neonates with HIE?

Identifying relevant studies

A comprehensive search strategy will be developed after consulting a librarian. The search will use various electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, Embase, the Cochrane database and CINAHL. Grey literature will also be included, with searches conducted across databases such as the WHO and the websites of paediatric associations. Additional sources, such as ministries of health websites, conference proceedings and reports from thesis and dissertation databases, will be explored. The search will cover studies published from 1990 to the date of the final search. There will be no language restrictions, though non-English studies will be translated whenever feasible. The search will combine Medical Subject Headings and free-text terms, as shown in table 1. Boolean operators, OR and AND, will be used to connect search terms.

Study selection

All the identified records will be uploaded to Covidence, an online screening tool.[26] Two reviewers will independently screen titles and abstracts against the inclusion criteria. The included studies will be evaluated and independently reviewed as full texts by the same reviewers. Any discrepancies at any stage will be resolved by a third reviewer. The screening and study selection process will

Table 1 Search strings to be used during the search

Database	Search strings
PubMed	(“Hypoxic-Ischemic Encephalopathy”(Mesh)) OR “hypoxic ischemic encephalopathy” OR HIE OR “birth asphyxia” OR “perinatal asphyxia”) AND (“Infant, Newborn”(Mesh)) OR neonate* OR newborn* OR “new born” OR neonatal) AND (“Seizures”(Mesh)) OR seizure* OR convulsion*) AND (prophylaxis OR prophylactic OR preventive OR prevention OR “pre-emptive” OR “preemptive”) AND (“Anticonvulsants”(Mesh)) OR “antiseizure medication*” OR “anti-seizure medication*” OR anticonvulsant* OR anti-epileptic* OR phenobarbital OR phenobarbitone OR levetiracetam OR phenytoin OR benzodiazepine* OR midazolam OR diazepam)
Scopus	TITLE-ABS-KEY (“hypoxic ischemic encephalopathy” OR HIE OR “birth asphyxia” OR “perinatal asphyxia”) AND TITLE-ABS-KEY (neonate* OR newborn* OR neonatal) AND TITLE-ABS-KEY (seizure* OR convulsion*) AND TITLE-ABS-KEY (prophylaxis OR prophylactic OR preventive OR prevention OR “pre-emptive” OR preemptive) AND TITLE-ABS-KEY (“antiseizure medication*” OR “anti-seizure medication*” OR anticonvulsant* OR anti-epileptic* OR phenobarbital OR phenobarbitone OR benzodiazepine* OR midazolam OR diazepam)
EMBASE	(“hypoxic ischemic encephalopathy”/exp OR “hypoxic ischemic encephalopathy” OR HIE OR “birth asphyxia”/exp OR “perinatal asphyxia”) AND (“newborn”/exp OR neonate* OR newborn* OR neonatal) AND (“seizure”/exp OR seizure* OR convulsion*) AND (“prophylaxis”/exp OR prophylaxis OR prophylactic OR prevention OR “preemptive therapy”) AND (“anticonvulsant agent”/exp OR “antiseizure medication” OR anticonvulsant* OR anti-epileptic* OR phenobarbital OR phenobarbitone OR levetiracetam OR benzodiazepine* OR midazolam OR diazepam)
CINAHL	(MH “Hypoxic Ischemic Encephalopathy” OR “hypoxic ischemic encephalopathy” OR HIE OR “birth asphyxia” OR “perinatal asphyxia”) AND (MH “Infant, Newborn” OR neonate* OR neonatal) AND (MH “Seizures+” OR seizure* OR convulsion*) AND (prophylaxis OR prophylactic OR preventive OR prevention OR preemptive OR “pre-emptive”) AND (MH “Anticonvulsants+” OR “antiseizure medication*” OR anticonvulsant* OR phenobarbital OR phenobarbitone OR levetiracetam OR phenytoin OR benzodiazepine* OR midazolam OR diazepam)

HIE, hypoxic-ischaemic encephalopathy; MH, Major Heading.

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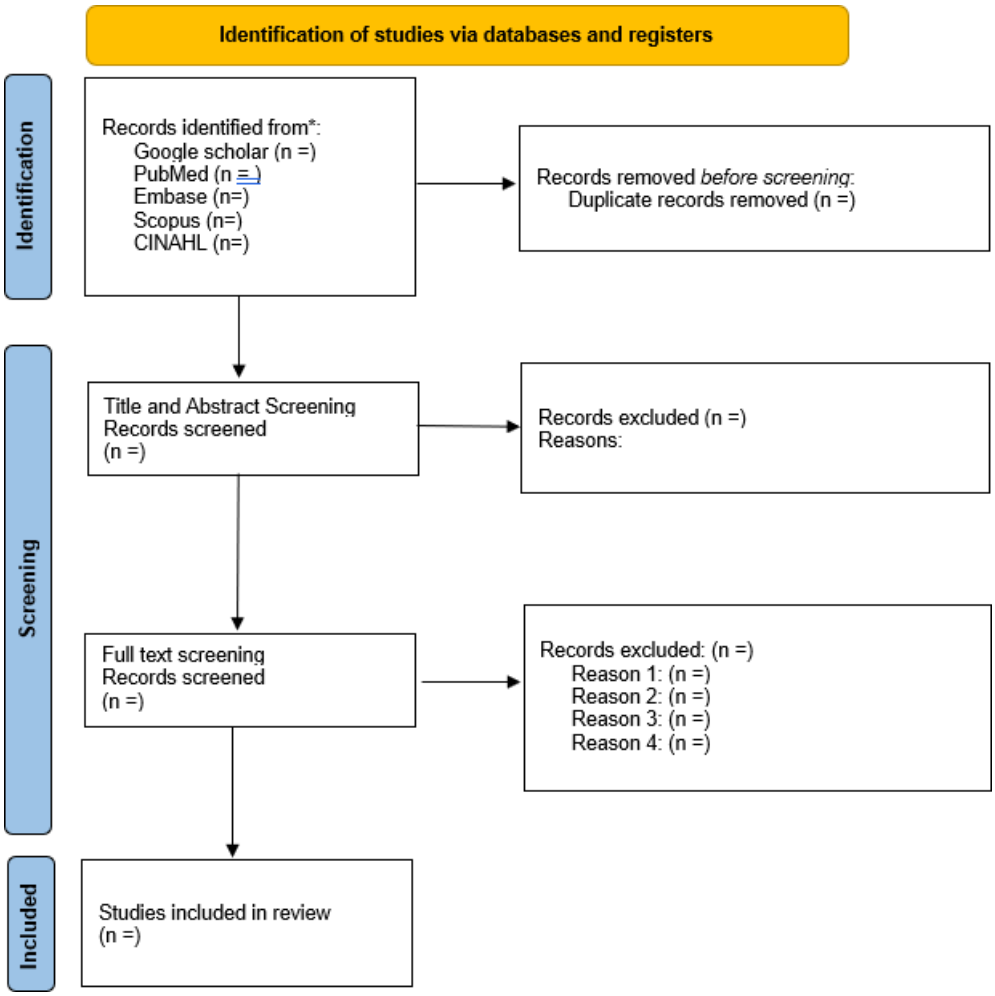


Figure 1 The PRISMA flow diagram that will be followed while selecting studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

be documented, and illustrations will be prepared using the PRISMA-ScR flow diagram (figure 1).[27]

Inclusion criteria

1. Studies involving prophylactic ASM use in HIE neonates.
2. Randomised controlled trials, cohort studies and case-control studies exploring prophylactic ASM among neonates with HIE.
3. Clinical guidelines and protocols exploring prophylactic ASM among neonates with HIE.
4. Observational and descriptive studies on prophylactic ASM among neonates with HIE.
5. Non-randomised trials about prophylactic ASM among neonates with HIE.
6. Treatment studies only if they capture the adverse effects of treatment.

Exclusion criteria

1. Studies focusing only on treatment without reporting treatment effects.
2. Animal studies.
3. Reviews, however, and references from these reviews will be screened manually.

Data extraction and reporting

Data will be charted using a data extraction tool that captures parameters such as study characteristics (author(s), year of publication, journal and country). Other details to be extracted will include infant baseline variables (gestational age, birth weight, HIE severity, HIE grading and duration of seizures), treatment characteristics (ASM regimen administered, duration of administration, presence or absence of therapeutic hypothermia and level of health facility) and outcome variables (short- and long-term outcomes). We will also extract information on potential confounders (whether ASMs were also used for treatment and for what proportion of infants and the presence or absence of treatment guidelines). Results will be presented in tables, charts and narrative summaries. Data extraction will be performed independently by two individuals to ensure that adequate information is extracted.

Critical appraisal

The methodological quality of empirical studies will be assessed independently by two reviewers using either the Mixed Methods Appraisal Tool (MMAT) 2018 or the

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JBI Critical Appraisal Checklist.[28 29] These checklists will be selected according to the study design, for example, cross-sectional, qualitative, cohort, case-control or mixed-methods. MMAT will be used because it allows appraisal of qualitative, quantitative and mixed-methods studies within a single framework.[29]

Current study status

The review has not yet commenced. Tentative dates for the initial search are set between October and November 2026.

Checklist

The PRISMA-ScR protocol checklist is included in online supplemental file 1.[27]

ETHICS AND DISSEMINATION

The study will use previously published information so ethical approval was not obtained. All included studies will be properly cited in accordance with their publication licences. The collected data will be summarised in a scoping review and submitted for publication in a peer-reviewed international journal. Additionally, the datasets will be made publicly accessible via a data repository such as the Open Science Framework.

DISCUSSION AND CONCLUSION

Globally, neonatal HIE continues to predispose to mortality and long-term neurodevelopmental issues, with a significant burden noted in low- and middle-income countries. Neonates with HIE grading II and III according to the Sarnat and Sarnat score are prone to experiencing seizures, and these often have worse prognostic features, such as cerebral palsy, cognitive decline and epilepsy.[2] One of the proven potential management strategies for reducing the effects of hypoxia and ischaemia is the administration of anticonvulsant medication, which helps minimise the brain's excitatory state.[30–32] However, most of these medications are to treat seizures and are often administered in the absence of monitoring modalities, for example, the continuous EEG. The absence of monitoring modalities predisposes to delayed seizure detection and treatment administration. Although ASMs are widely used in the management of neonatal seizures associated with HIE, important uncertainties remain regarding the extent of clinical benefit associated with different seizure treatment thresholds and monitoring strategies. Emerging evidence suggests that the relationship between seizure suppression, electrographic seizure burden, neurodevelopmental outcomes and potential medication-related toxicity remains incompletely understood.[33] Questions also persist regarding the management of electrographic-only seizures and the optimal balance between early seizure control and avoidance of unnecessary ASM exposure. These uncertainties further highlight the importance of comprehensively mapping existing evidence on prophylactic ASM use in neonates with HIE.

Some evidence has proposed the use of ASM as prophylaxis, especially among babies who have experienced asphyxia.[34 35] The theoretical rationale for prophylactic ASM administration is grounded in the concept of preventing secondary brain injury caused by recurrent or prolonged seizures. But the use of ASM as prophylaxis among asphyxiated babies has rarely been documented, is controversial and, if done, is poorly standardised. Prophylactic antiseizure therapy can expose infants to unnecessary medication harms, so careful evaluation of adverse outcomes is crucial. This is especially important in infants with mild HIE, where seizure risk is lower, and other diagnoses should be considered. The review will also map evidence regarding both acute and long-term adverse effects associated with prophylactic ASM use. Additionally, most studies exploring this practice have been animal studies, with few trials and no interventional studies.[18 19 36] This review will therefore be critical in synthesising available data on both efficacy and safety outcomes, including seizure incidence, mortality and long-term neurodevelopment. The evidence obtained will identify existing gaps, highlight inconsistencies and inform the design of future studies, such as clinical trials and comparative studies. It will also support the development of evidence-based guidelines for neonatal seizure management.

Contributors ELN and IA conceptualised the protocol and will coordinate its conduct. TDE provided technical input to the paper. IA is the guarantor.

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