



Neonatal Seizures – Neonatal – Impatient/Emergency Department Clinical Practice Guideline

Note: Active Table of Contents – Click each header below to jump to the section of interest

Table of Contents

INTRODUCTION.....	3
SCOPE.....	3
DEFINITIONS	3
RECOMMENDATIONS.....	4
METHODOLOGY.....	6
COLLATERAL TOOLS & RESOURCES	8
APPENDIX A. MANAGEMENT OF NEONATAL SEIZURE	9
REFERENCES.....	10

Content Expert:

Name: Monica Bogenschutz, PharmD, BCPPS, BCPS – Pharmacy

Phone Number: (608) 422-8164

Email Address: mbogenschutz@uwhealth.org

Contact for Changes:

Name: Philip Trapskin, PharmD, BCPS – Pharmacy

Phone Number: (608) 263-1328

Email Address: ptrapskin@uwhealth.org

Guideline Author:

Jenna Bender, PharmD, BCPPS – Pharmacy

Workgroup Members:

Jenna Bender, PharmD, BCPPS

Monica Bogenschutz, PharmD, BCPPS, BCPS

Joshua Vanderloo, PharmD, BCPS

Reviewers:

Andrew Knox, MD – Pediatric Neurology

Jamie Limjoco, MD – Neonatology

Adam Wallace, MD – Pediatric Neurology

David Yang, MD – Laboratory

Committee Approvals:

Pharmacy & Therapeutics Committee, July 2018

Introduction

The risk for seizures is highest in the neonatal period, occurring in 1.8 to 3.5/1,000 neonates.¹ There is growing evidence that neonatal seizures may contribute to adverse neurodevelopmental outcomes leading to the need for safe and effective treatment options.²⁻⁴ Historical first-line treatment for neonatal seizures has been with phenobarbital.⁵ However, data suggests phenobarbital efficacy in only 30% to 50% of neonates and a Cochrane Review concluded that there is little evidence to support the use of any antiepileptic drugs (AEDs) in the neonatal period.⁶⁻⁸ With the lack of robust literature and the safety concerns associated with the use of phenobarbital, there has been a decrease in phenobarbital utilization and a significant increase in levetiracetam utilization.⁵

In humans, in utero exposure to phenytoin, phenobarbital, valproate, and/or carbamazepine has been shown to be associated with lower intellectual functioning, and children treated with phenobarbital for febrile seizures in the first three years of life years have decreased IQ compared to matched controls.⁹⁻¹³ In multiple animal studies in both rats and primates, phenytoin and phenobarbital have been shown to cause neuronal apoptosis in the first weeks of life as well as affect other aspects of brain development such as synaptic maturation.¹⁴ In contrast, levetiracetam has been shown not to lead to apoptosis in rats at any dose, nor has topiramate at therapeutic doses.^{15,16} A recent study by Maitre and colleagues found that exposure to phenobarbital was associated with worse outcomes at two years of age and that levetiracetam may be associated with improved outcomes when compared to phenobarbital.¹⁷

The risk of morbidity from seizures, the risk of morbidity from a particular AED, and the expected efficacy of that AED must all be considered when treating neonatal seizures. There is not a large body of literature assessing levetiracetam as the first-line agent for the treatment of neonatal seizures, but there are multiple studies showing phenobarbital followed by levetiracetam is well tolerated and efficacious.¹⁸⁻²² Based on this literature and our expert opinion, this guideline will focus on using levetiracetam as the first-line agent for the treatment of neonatal seizures.

Scope

Intended Users:

Pediatric physicians (residents, fellows, and attendings), Advanced Practice Providers, Nurses, Pharmacists, Respiratory Therapists

Objective:

To decrease unintended variability in caregiver practice and to minimize delays in providing care to neonatal patients with concern for seizures, by providing guidance and evidence-based recommendations for the acute evaluation and management of neonatal seizures.

Target Population:

This guideline targets neonatal patients with a PMA younger than 48 weeks presenting with concern for seizures or at high risk for seizures. For patients with a PMA greater than 48 weeks refer to [Status Epilepticus – Pediatric – Emergency Department/Inpatient Clinical Practice Guideline](#).

Clinical Questions Considered:

- What is the initial medication strategy for neonates having seizure?
- What are the therapies for refractory seizure?
- How should neonates receiving therapy for seizure be monitored?

Definitions

1. **Neonatal seizures** should be defined as paroxysmal alterations in neurologic function (e.g. behavioral, motor, or autonomic function) due to abnormal excessive or synchronous neuronal activity in the brain.^{23,24}
 - a. While there is no standard definition for neonatal seizures, there is consensus that diagnosis relies on confirmatory EEG characteristics.

Recommendations

Goals of Treatment

1. The treatment of neonatal seizures should occur rapidly and continue sequentially until seizures are halted or there is a sustained response with less than a 10% seizure burden over a four-hour period. (*UW Health Conditional recommendation, very low quality evidence*)
2. Critical care treatment and monitoring should be started simultaneously with emergent initial therapy and continued until further therapy is successful or futile. (*UW Health Strong recommendation, very low quality evidence*)

General Initial Treatment Considerations

1. The etiology of neonatal seizures should be diagnosed and treated as soon as possible. (*UW Health Strong recommendation, very low quality evidence*)
2. Levetiracetam should be given as first-line therapy.^{18,19,25} (*UW Health Conditional recommendation, low quality evidence*)
3. Pediatric Neurology should be consulted. (*UW Health Strong recommendation, very low quality evidence*)
4. Benzodiazepines should be the drug of choice in the instance that levetiracetam will not be available within the appropriate timeframe. (*UW Health Conditional recommendation, very low quality evidence*)
 - 4.1. Lorazepam is the drug of choice for intravenous administration. (*UW Health Conditional recommendation, very low quality evidence*)
5. Phenobarbital should be given as second-line therapy.^{8,26} (*UW Health Strong recommendation, moderate quality evidence*)

Treatment Timeline

1. **Zero to 5 minutes** – Rapid assessment of neonate presenting with seizures by MD and RN
 - 1.1. Assess and support airway, breathing, and circulation and apply appropriate monitoring devices (continuous cardiac rhythm monitoring, continuous pulse oximetry, VEEG) (*UW Health Strong Recommendation, very low quality evidence*)
 - 1.2. Note time of seizure onset and clinical presentation through documentation as a progress note in the electronic medical record. (*UW Health Strong Recommendation, very low quality evidence*)
 - 1.3. Establish IV or IO access. (*UW Health Strong Recommendation, very low quality evidence*)
 - 1.4. Assess POC glucose and correct hypoglycemia if present.²⁷ (*UW Health Conditional Recommendation, moderate quality evidence*)
 - 1.4.1. For peripheral or central access: dextrose 10% intravenous 2 mL/kg over 5 minutes.²⁸ (*UW Health Conditional Recommendation, moderate quality evidence*)
 - 1.5. Assess electrolyte abnormalities and correct if necessary.²⁷ (*UW Health Conditional Recommendation, moderate quality evidence*)
 - 1.5.1. Most commonly contributing abnormalities in neonatal population include hypocalcemia, hypo- or hypernatremia, and hypomagnesemia.²³
 - 1.6. Assess physical examination, including neurologic examination. (*UW Health Strong Recommendation, very low quality evidence*)
 - 1.7. Acquire laboratory samples, including, but not limited to (*UW Health Conditional recommendation, low quality evidence*):
 - Serum electrolytes: sodium, potassium, chloride, bicarbonate, calcium (total and ionized), and magnesium
 - Blood urea nitrogen and creatinine
 - Complete blood count with differential
 - Antiepileptic drug concentrations, if deemed necessary by discussion with Pediatric Neurology and Pharmacy
 - Other labs that may be warranted depending on presentation include blood culture, urine culture, liver function tests, coagulation panels, genetic labs for assessment of inborn errors of metabolism, or toxicology screen.
 - 1.8. Consult Pediatric Neurology. (*UW Health Strong recommendation, very low quality evidence*)

2. First-line treatment, after 5 minutes of seizure

- 2.1. The first drug administered should be levetiracetam.^{18,19} (*UW Health Conditional recommendation, low quality evidence*)
 - 2.1.1. First intravenous loading dose: levetiracetam 50 mg/kg over 15 minutes.^{20,29,30} (*UW Health Conditional Recommendation, low quality evidence*)
 - 2.1.2. If seizures are confirmed on EEG, a second loading dose of levetiracetam should be administered and maintenance levetiracetam should be initiated. (*UW Health Conditional recommendation, very low quality evidence*)
 - 2.1.2.1. Second intravenous loading dose: levetiracetam 50 mg/kg once over 15 minutes.^{20,29,30}
 - 2.1.2.2. Intravenous or oral maintenance dose: levetiracetam 25 mg/kg twice daily.^{29,30}
 - 2.1.2.3. Maintenance dose should start six to twelve hours after last intravenous loading dose.
- 2.2. If levetiracetam is not available to administer within 10 minutes, may consider administration of lorazepam. (*UW Health Conditional recommendation, very low quality evidence*)
 - 2.2.1. Intravenous: lorazepam 0.1 mg/kg over 2 minutes, maximum of two doses. (*UW Health Conditional Recommendation, very low quality evidence*)

3. Second-line treatment, allow 30 minutes after last levetiracetam loading dose

- 3.1. The next drug to be administered should be phenobarbital.^{8,26} (*UW Health Strong recommendation, moderate quality evidence*)
 - 3.1.1. First intravenous loading dose: phenobarbital 20 mg/kg over 15-30 minutes.^{31,32} (*UW Health Conditional recommendation, low quality evidence*)
 - 3.1.1.1. Adverse effects of phenobarbital include respiratory depression and hypotension and may necessitate airway and circulatory support.
- 3.2. If seizures continue, may administer up to two further doses of 10 mg/kg (maximum of 40 mg/kg total).^{31,32} (*UW Health Conditional recommendation, low quality evidence*)
 - 3.2.1. If improvement seen after an additional loading dose of phenobarbital, maintenance should be initiated. (*UW Health Conditional recommendation, very low quality evidence*)
 - 3.2.1.1. Intravenous or oral maintenance dose: phenobarbital 2.5 mg/kg twice daily.
 - 3.2.1.2. Maintenance dose should start twelve hours after last intravenous loading dose.

4. Refractory treatment

- 4.1. The next drug administered may be fosphenytoin.^{8,32} (*UW Health Conditional recommendation, very low quality evidence*)
 - 4.1.1. First intravenous loading dose: fosphenytoin 20 mg PE/kg given no faster than 2 mg PE/kg/min (maximum 150 mg PE/min; where PE is phenytoin equivalents).
 - 4.1.2. If seizures continue, may give another 10 mg PE/kg if seizures persist
 - 4.1.3. Monitor for adverse effects of fosphenytoin and phenytoin including cardiac arrhythmia and hypotension, as well as nystagmus and ataxia as these may be signs of supratherapeutic concentrations
- 4.2. Other options to consider based on discussion with Pediatric Neurology include pyridoxine, midazolam continuous infusion, topiramate, or lidocaine infusion. (*UW Health Conditional recommendation, very low quality evidence*)

General Considerations Following Initial Seizure Management

1. Video EEG should be used to identify neonatal seizures as vEEG is able to discern true seizure activity from other clinical presentations which appear similar to seizures but are not seizures.³³ (*UW Health Strong recommendation, high quality evidence*)
2. In cases of renal insufficiency, dose adjustments for levetiracetam should be discussed with neonatologists, neurologists and pharmacists. (*UW Health Strong recommendation, very low quality evidence*)
3. Drug concentration monitoring
 - 3.1. Levetiracetam: there is insufficient data regarding clinical utility of these levels and dosing adjustments based upon therapeutic drug monitoring. Concentration reference ranges are not

- adequately described in neonates to correlate with efficacy.^{21,34} (*UW Health Conditional recommendation, low quality evidence*)
- 3.2. Phenobarbital: trough goal 15 to 40 mcg/mL.
 - 3.2.1. Consider obtaining prior to starting maintenance therapy.⁸ (*UW Health Conditional Recommendation, low quality evidence*)
 - 3.3. Free phenytoin: two-hour goal 1-2 mg/dL.
 - 3.3.1. Free phenytoin concentration is recommended in addition to total phenytoin concentration in the neonatal population as total phenytoin concentrations poorly predict free phenytoin concentrations in the critically ill pediatric patient.³⁵ (*UW Health Conditional Recommendation, low quality evidence*)
 4. Continue EEG monitoring until seizure free for 24 hours (*UW Health Conditional recommendation, very low quality evidence*)
 5. If etiology of seizures was hypoxic ischemic injury (HIE), consider discussing discontinuation of anti-epileptics (AEDs) after seven days if patient is free of seizures. (*UW Health Conditional recommendation, very low quality evidence*)
 6. All patients with spells concerning of seizures should be evaluated with EEG until: (*UW Health Conditional recommendation, very low quality evidence*)
 - Patient is 24 hours seizure free; this may be extended at Neonatology or Pediatric Neurology discretion for patients at high risk for seizures based on history or EEG findings or when seizures may not be detected on clinical exam (i.e. paralyzed patients);
 - Events are shown not to be seizure;
 - Cooling protocol is completed for HIE patients

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Methodology

Development Process

Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:

The following criteria were used by the guideline author and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:

- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

Time Period: 1990 to 2018

Search Terms: The following is a list of various search terms that were used individually or in combination with each other for literature searches on PubMed: neonatal, neonates, seizures, phenobarbital, levetiracetam, neonatal seizures, pharmacokinetics, therapeutic drug monitoring.

Methods to Select the Evidence:

Literary sources were selected with the following criteria in though: English language, publication in a MEDLINE core clinical journal, and strength of expert opinion.

Methods Used to Formulate the Recommendations:

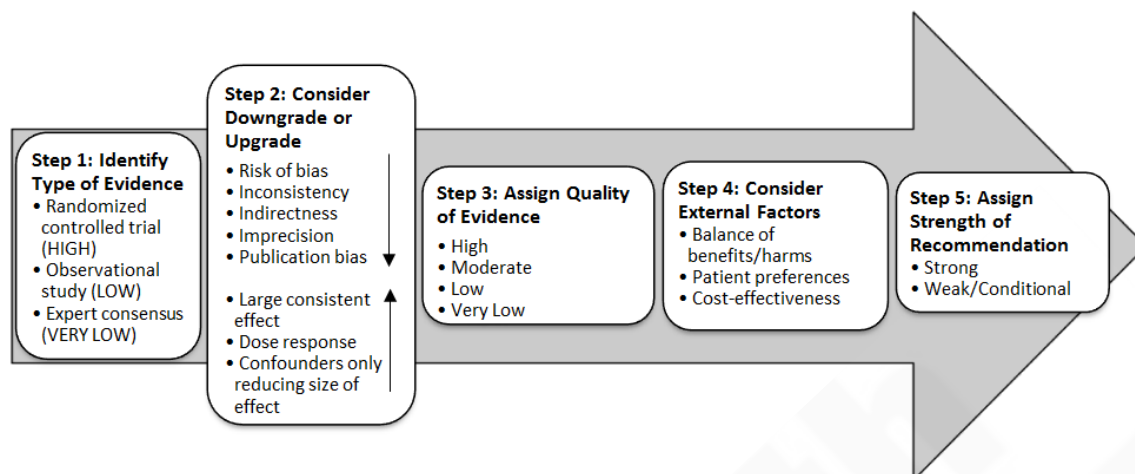
The workgroup members created recommendations internally through a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:

Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1**).

Figure 1. GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

Recognition of Potential Health Care Disparities: None identified

Collateral Tools & Resources

Metrics

1. Time of onset of seizure to administration of levetiracetam
2. Number of patients receiving benzodiazepine prior to levetiracetam
3. Number of patients proceeding to receive phenobarbital
4. Documentation of seizure start time and duration in Health Link
5. Documentation of point-of-care glucose measurement

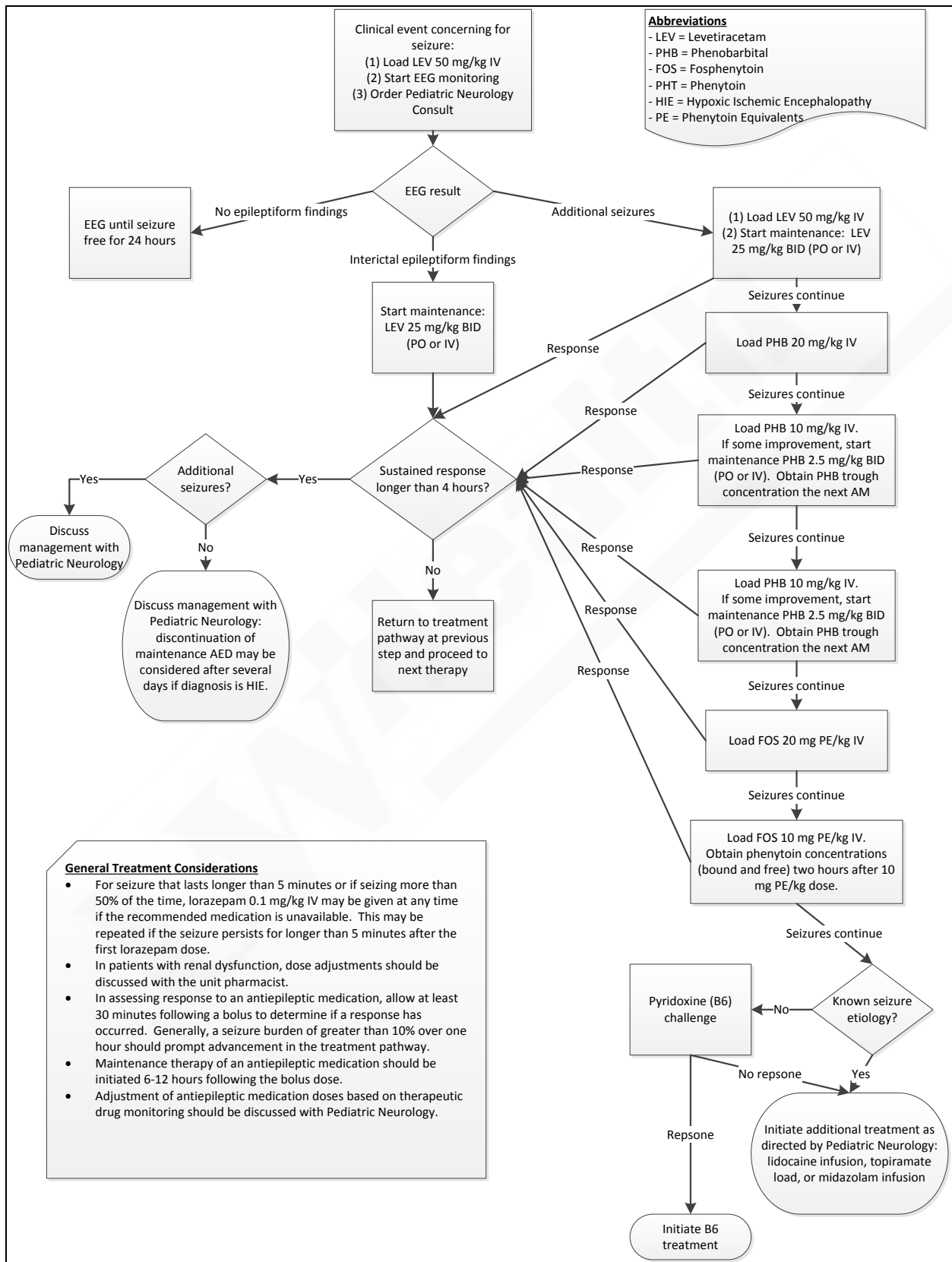
Patient Resources

1. [Health Facts for You #7351 – Intranasal Midazolam to Treat Seizures in the Hospital](#)
2. [Health Facts for You #7358 – Intranasal Midazolam to Treat Seizures in the Hospital \(Spanish\)](#)
3. [Health Information: Seizures](#)

Policies

1. [UW Health Policy 6.10AP- Care of Patient With or at Risk For Seizure \(Adult & Pediatric\)](#)

Appendix A. Management of Neonatal Seizure



References

1. Silverstein FS, Jensen FE. Neonatal seizures. *Ann Neurol*. Aug 2007;62(2):112-120.
2. van Rooij LG, van den Broek MP, Rademaker CM, de Vries LS. Clinical management of seizures in newborns : diagnosis and treatment. *Paediatr Drugs*. Feb 2013;15(1):9-18.
3. Glass HC, Sullivan JE. Neonatal seizures. *Curr Treat Options Neurol*. Nov 2009;11(6):405-413.
4. Kharoshankaya L, Stevenson NJ, Livingstone V, et al. Seizure burden and neurodevelopmental outcome in neonates with hypoxic-ischemic encephalopathy. *Dev Med Child Neurol*. Dec 2016;58(12):1242-1248.
5. Ahmad KA, Desai SJ, Bennett MM, et al. Changing antiepileptic drug use for seizures in US neonatal intensive care units from 2005 to 2014. *J Perinatol*. Mar 2017;37(3):296-300.
6. Slaughter LA, Patel AD, Slaughter JL. Pharmacological treatment of neonatal seizures: a systematic review. *J Child Neurol*. Mar 2013;28(3):351-364.
7. Booth D, Evans DJ. Anticonvulsants for neonates with seizures. *Cochrane Database Syst Rev*. Oct 18 2004(4):CD004218.
8. Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med*. Aug 12 1999;341(7):485-489.
9. Levitt P, Harvey JA, Friedman E, Simansky K, Murphy EH. New evidence for neurotransmitter influences on brain development. *Trends Neurosci*. Jun 1997;20(6):269-274.
10. Losche G, Steinhausen HC, Koch S, Helge H. The psychological development of children of epileptic parents. II. The differential impact of intrauterine exposure to anticonvulsant drugs and further influential factors. *Acta Paediatr*. Sep 1994;83(9):961-966.
11. Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. *Jama*. Mar 9 1994;271(10):767-770.
12. Vinten J, Adab N, Kini U, Gorry J, Gregg J, Baker GA. Neuropsychological effects of exposure to anticonvulsant medication in utero. *Neurology*. Mar 22 2005;64(6):949-954.
13. Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures--effects on intelligence and on seizure recurrence. *N Engl J Med*. Feb 8 1990;322(6):364-369.
14. Bittigau P, Sifringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci U S A*. Nov 12 2002;99(23):15089-15094.
15. Manthey D, Asimiadou S, Stefovska V, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. *Exp Neurol*. Jun 2005;193(2):497-503.
16. Glier C, Dzielko M, Bittigau P, Jarosz B, Korobowicz E, Ikonomidou C. Therapeutic doses of topiramate are not toxic to the developing rat brain. *Exp Neurol*. Jun 2004;187(2):403-409.
17. Maitre NL, Smolinsky C, Slaughter JC, Stark AR. Adverse neurodevelopmental outcomes after exposure to phenobarbital and levetiracetam for the treatment of neonatal seizures. *J Perinatol*. Nov 2013;33(11):841-846.
18. McHugh DC, Lancaster S, Manganas LN. A Systematic Review of the Efficacy of Levetiracetam in Neonatal Seizures. *Neuropediatrics*. Feb 2018;49(1):12-17.
19. Falsaperla R, Vitaliti G, Mauceri L, et al. Levetiracetam in Neonatal Seizures as First-line Treatment: A Prospective Study. *J Pediatr Neurosci*. Jan-Mar 2017;12(1):24-28.
20. Venkatesan C, Young S, Schapiro M, Thomas C. Levetiracetam for the Treatment of Seizures in Neonatal Hypoxic Ischemic Encephalopathy. *J Child Neurol*. Feb 2017;32(2):210-214.
21. Sharpe CM, Capparelli EV, Mower A, Farrell MJ, Soldin SJ, Haas RH. A seven-day study of the pharmacokinetics of intravenous levetiracetam in neonates: marked changes in pharmacokinetics occur during the first week of life. *Pediatr Res*. Jul 2012;72(1):43-49.
22. Merhar SL, Schibler KR, Sherwin CM, et al. Pharmacokinetics of levetiracetam in neonates with seizures. *J Pediatr*. Jul 2011;159(1):152-154 e153.
23. Hill A. Neonatal seizures. *Pediatr Rev*. Apr 2000;21(4):117-121.
24. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. Apr 2017;58(4):522-530.
25. Furwentsches A, Bussmann C, Ramantani G, et al. Levetiracetam in the treatment of neonatal seizures: a pilot study. *Seizure*. Apr 2010;19(3):185-189.
26. Boylan GB, Rennie JM, Chorley G, et al. Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. *Neurology*. Feb 10 2004;62(3):486-488.
27. WHO/ILAE/IRCCS. Guidelines on neonatal seizures. World Health Organization website. http://www.who.int/mental_health/publications/guidelines_neonatal_seizures/en/. Updated 2011. Accessed July 10, 2018.
28. Hegenbarth MA. Preparing for pediatric emergencies: drugs to consider. *Pediatrics*. Feb 2008;121(2):433-443.
29. Khan O, Chang E, Cipriani C, Wright C, Crisp E, Kirmani B. Use of intravenous levetiracetam for management of acute seizures in neonates. *Pediatr Neurol*. Apr 2011;44(4):265-269.

30. Khan O, Cipriani C, Wright C, Crisp E, Kirmani B. Role of intravenous levetiracetam for acute seizure management in preterm neonates. *Pediatr Neurol.* Nov 2013;49(5):340-343.
31. Low E, Stevenson NJ, Mathieson SR, et al. Short-Term Effects of Phenobarbitone on Electrographic Seizures in Neonates. *Neonatology.* 2016;110(1):40-46.
32. Pathak G, Upadhyay A, Pathak U, Chawla D, Goel SP. Phenobarbitone versus phenytoin for treatment of neonatal seizures: an open-label randomized controlled trial. *Indian Pediatr.* Aug 2013;50(8):753-757.
33. Wietstock SO, Bonifacio SL, Sullivan JE, Nash KB, Glass HC. Continuous Video Electroencephalographic (EEG) Monitoring for Electrographic Seizure Diagnosis in Neonates: A Single-Center Study. *J Child Neurol.* Mar 2016;31(3):328-332.
34. Agrawal A, Banergee A. A Review on Pharmacokinetics of Levetiracetam in Neonates. *Curr Drug Metab.* Oct 16 2017;18(8):727-734.
35. Wolf GK, McClain CD, Zurakowski D, Dodson B, McManus ML. Total phenytoin concentrations do not accurately predict free phenytoin concentrations in critically ill children. *Pediatr Crit Care Med.* Sep 2006;7(5):434-439; quiz 440.