This guideline has been prepared with reference to the following:

Venkatesan C, Young S, Schapiro M, et al. Levetiracetam for the Treatment of Seizures in Neonatal Hypoxic Ischemic Encephalopathy. J Child Neurol 2017;32:210–4

Ramantani G, Ikonomidou C, Walter B, et al. Levetiracetam: safety and efficacy in neonatal seizures. Eur J Paediatr Neurol 2011;15:1–7

Fürwentsches A, Bussmann C, Ramantani G, et al. Levetiracetam in the treatment of neonatal seizures: a pilot study. Seizure 2010;19:185–9

How efficacious and safe is levetiracetam for the treatment of neonatal seizures?
A 2021 systematic review assessed the effectiveness and safety of levetiracetam when used as first-line treatment of neonatal seizures (Hooper, 2021). Fourteen studies assessing 1188 neonates were included: four RCTs, three observational trials. Pooled efficacy of levetiracetam from observational studies was 45% (95% confidence interval [CI] 34 to 57%). Meta-analysis of RCTs evaluating levetiracetam versus phenobarbital showed that both were equally effective (risk ratio [95% CI] 0.6 [0.30 to 1.20]). Levetiracetam resulted in a lower risk of short-term adverse events compared to phenobarbital (risk ratio [95% CI] 0.24 [0.06 to 0.92]). The authors concluded that very low certainty of evidence suggests levetiracetam might not be more effective than phenobarbital and that moderate certainty of evidence indicates levetiracetam is associated with a lower risk of adverse events.
A 2018 systematic review found that complete or near-complete seizure cessation was achieved as follows: primary levetiracetam 37/48 (77%), secondary levetiracetam 34/54 (63%) [McHigh, 2018]. This compared with primary phenobarbital 24/52 (46%). The review authors concluded that that levetiracetam may be at least as or more effective for neonatal seizures as phenobarbital.

Hooper RG, Ramaswamy VV, Wahid RM et al. Levetiracetam as the first-line treatment for neonatal seizures: a systematic review and meta-analysis. Dev Med Child Neurol. 2021;63:1283-93

McHugh DC, Lancaster S, Manganas LN. A Systematic Review of the Efficacy of Levetiracetam in Neonatal Seizures. Neuropediatrics. 2018;49:12-7

Evidence Level: I

When should term or preterm neonates with convulsions be treated with drugs (phenobarbitone, phenytoin, clonazepam or midazolam) and when should these be stopped?
The duration of convulsions or seizures in the neonate may be brief and the signs subtle, making it difficult to decide when drug treatment should be started and stopped. As a generalisation, most neonatologists treat if more than 3 brief seizures occur in an hour, or a single seizure lasts more than 3 minutes (Rennie, 1999).
Neonatal convulsions are resistant to most standard antiepileptic drugs (Sankar, 2005; Booth, 2004; Zupanc, 2003), with, for example, phenobarbitone being effective as a first-line treatment in only around one-third of cases (Rennie, 2003). A study in 59 neonates comparing phenobarbitone and phenytoin (Painter, 1999) found that the two drugs were equally effective, but that each failed to control seizures in more than half of cases when administered alone. Failure is often associated with a significantly abnormal background EEG (Boylan, 2002).
Phenytoin as a second-line treatment is generally more effective than a benzodiazepine, although large evaluation studies are lacking (Rennie, 2003).
Nasal midazolam stopped 122 of 125 seizures (98%) within 10 minutes (average 3.6 min) in a small study involving 26 children both in and out of hospital (Jeannet, 1999). In another study, in 6 neonates whose convulsions were refractory to high-dose phenobarbitone and phenytoin (Sheth, 1996), midazolam controlled the seizures in all 6 within 1 hour.
In a small retrospective study (Brod, 1988), a normal EEG was found to be a reliable predictor for discontinuing drug treatment in 18 of 22 term infants and 9 of 10 premature infants.
As long-term use of phenobarbitone is associated with impaired cognitive function in infants and toddlers, and the risk of recurrent seizures is less than 10% in the absence of neurologic damage, early discontinuation of treatment is advisable (Hellstrom, 1995; Gal, 1985).

Booth D, Evans DJ. Anticonvulsants for neonates with seizures. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004218
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004218.pub2/full

Boylan GB, Rennie JM, Pressler RM, et al. Phenobarbitone, neonatal seizures, and video-EEG. Arch Dis Child Fetal Neonatal Ed 2002;86:F165-70
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1721395/pdf/v086p0F165.pdf

Brod SA, Ment LR, Ehrenkranz RA, et al. Predictors of success for drug discontinuation following neonatal seizures. Pediatr Neurol 1988;4:13-7

Gal P. Anticonvulsant therapy after neonatal seizures: how long should it be continued? 1. A case for early discontinuation of anticonvulsants. Pharmacotherapy 1985;5:268-73

Hellstrom WL, Blennow G, Lindroth M, et al. Low risk of seizure recurrence after early withdrawal of antiepileptic treatment in the neonatal period. Arch Dis Child Fetal Neonatal Ed 1995;72:F97-101
http://fn.bmj.com/content/72/2/F97.long

Jeannet PY, Roulet E, Maeder IM, et al. Home and hospital treatment of acute seizures in children with nasal midazolam. Eur J Paediatr Neurol 1999;3:73-7
http://archpedi.jamanetwork.com/article.aspx?articleid=383593

Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med 1999;341:485-9
http://www.nejm.org/doi/full/10.1056/NEJM199908123410704#t=articleTop

Rennie JM. Seizures in the newborn. In: Rennie JM, Roberton NR (eds). Textbook of neonatology, 3rd ed . Edinburgh, Churchill Livingstone, 1999. p1219

Rennie JM., Boylan GB. Neonatal seizures and their treatment. Curr Opin Neurol 2003;16:177-81

Sankar R, Painter MJ. Neonatal seizures: after all these years we still love what doesn't work. Neurology 2005;64:776-7

Sheth RD, Buckley DJ, Gutierrez, AR, et al. Midazolam in the treatment of refractory neonatal seizures. Clin Neuropharmacol 1996;19:165-70

Zupanc ML. Infantile spasms. Expert Opin Pharmacother 2003;4:2039-48

Evidence Level: IV

Last amended December 2021
Last reviewed December 2021