# Drug Treatment of Seizures and Epilepsy in Newborns and Children

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**KEYWORDS**

• Anticonvulsant • Antiepileptic • Anti-seizure medication • Epilepsy • Pediatric

**KEY POINTS**

- Many new antiepileptic drugs (AEDs) are available.
- Few AEDs are systematically evaluated in children and even fewer in neonates and infants.
- Off-label AEDs use is frequent in children.
- Minimal comparative efficacy data are available.
- Identification of specific genetic epilepsy mechanisms may enable future development of a precision medicine approach to guide drug treatment.

## INTRODUCTION

Epilepsy is a common and heterogeneous pediatric disorder characterized as a chronic predisposition to seizures. The estimated lifetime prevalence of epilepsy is approximately 1%, with onset mostly in early childhood and in the elderly.[1] Epilepsy has been traditionally diagnosed based on a history of 2 or more unprovoked seizures spaced greater than 24 hours apart. Recently, the definition has been expanded to include individuals who have had a single unprovoked seizure but who have a greater than 60% chance of additional seizures occurring over the next 10 years.[2] In clinical practice, risk prediction for additional seizures is most commonly based on identification of specific electroencephalography (EEG) patterns.

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Epilepsies are classified by their associated seizure types (eg, focal vs generalized) and etiology.[3] At times, the constellation of seizure types, EEG findings, and age-dependent features (onset and remission) fit a recognized epilepsy syndrome. Readers are referred to standard texts and relevant review articles for detailed discussions of epilepsy classification, etiology, diagnostic evaluation, and prognosis.[4–7] Acute symptomatic seizures, febrile seizures, and status epilepticus may be associated with epilepsy but are distinct entities and treatment of these conditions is not covered in this article; they are covered in other reviews.[8]

The mainstay of medical treatment of epilepsy is prophylactic administration of medications, collectively described as antiepileptic drugs (AEDs), that can reduce the risk of seizure recurrence.[4,9–11] In 1993, there were approximately 7 AEDs that were commonly used to treat epilepsy; since then, many additional drugs have been developed and Food and Drug Administration (FDA) approved. These new-generation AEDs are broadly viewed as better than older AEDs with respect to having fewer adverse effects and drug interactions while retaining efficacy similar to older AEDs, such as carbamazepine and phenytoin. The goal of this article is to provide pediatricians with an overview of AEDs currently used to treat epilepsy in children, with a focus on guiding principles for drug therapy and recently introduced medications.

## OVERVIEW

### *Starting Antiepileptic Drug Treatment*

The history, neurologic examination, results of EEG and other neurodiagnostic tests, medical comorbidities, patient and family preference, and physician perspective all influence a decision to start AED treatment after a single unprovoked seizure, because estimates vary regarding the recurrence risk.[12] A recent Cochrane review concluded, "treatment of the first unprovoked seizure reduces the risk of a subsequent seizure but does not affect the proportion of patients in remission in the long-term," and there is no evidence of reduced mortality with AED treatment.[13] After a second unprovoked seizure, however, clinicians usually recommend starting an AED.[4,14,15]

Although more than 20 AEDs are currently FDA approved (**Tables 1** and **2**), in clinical practice, initial treatment options for infants and children include fewer agents (discussed later). Factors that influence drug selection include seizure and EEG classification (generalized vs focal vs specific epilepsy syndrome), drug formulation (liquid or chewable tablet vs capsule, convenience of dosing, **Table 3**), adverse-effect profile (**Table 4**), and clinician preferences.

Many of the older agents (see **Table 1**) are now prescribed less frequently in the United States, although they remain in wide use, particularly in low-resource settings. Perceived advantages of the newer drugs include greater convenience (no routine blood testing), broader spectrum (in particular for levetiracetam), fewer serious adverse effects, and fewer drug interactions.

As is the case for treatment of many of the pediatric disorders discussed in this issue, off-label treatment is common for children with epilepsy. Clinicians are generally comfortable extrapolating efficacy results from studies performed in adults to predict treatment responses in children; safety concerns and adverse effect profiles limit extrapolation to the youngest age groups.

Generic AED substitution has become a hot-button topic for clinicians and patients.[16] Although bioequivalence is difficult to document, recent studies and clinical experience suggest that generic substitution is feasible for many patients. Prescribers commonly recommend against switching among generic preparations, but this goal is sometimes challenging to attain in practice.