Nonfebrile Seizures
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Nonfebrile Seizures
Robert H. A. Haslam, MD*

**IMPORTANT POINTS**

1. Precise classification of seizure type is important for selecting the most appropriate anticonvulsant and providing an accurate prognosis.
2. Anticonvulsant therapy is not advised for the neurologically normal child following the first nonfebrile seizure if he or she has a negative electroencephalogram and no family history of epilepsy among first-degree relatives.
3. Phenobarbital and primidone are anticonvulsants that are most likely to produce untoward behavioral and cognitive side effects in children treated for epilepsy.
4. A history of an aura (epigastric discomfort, frightened feeling) indicates that the seizure has a focal onset.
5. Of those children who remain seizure-free for 2 years and have no risk factors, approximately 75% will remain free of seizures following withdrawal of the anticonvulsant.

Nonfebrile seizures occur in children of all ages and often pose a challenge to the pediatrician in terms of cause, management, and prognosis. The term “seizure” does not imply a diagnosis, but rather indicates a clinical event that reflects a time-related dysfunction of the central nervous system (CNS) and may signal a serious underlying abnormality; however, more often in children the term indicates a transient disturbance of brain function. The pediatrician’s role is to determine the cause of the seizure and to treat the condition, based on an understanding of its pathogenesis, impact on the child and family, and the long-term outlook of the condition.

Seizures and epilepsy are not synonymous. A seizure (convulsion) is defined as a paroxysmal involuntary discharge of cortical neurons that may be manifested clinically by an impairment or loss of consciousness, abnormal motor activity, behavioral and emotional abnormalities, sensory disturbances, or autonomic dysfunction. Some seizures are characterized by abnormal movements without loss of consciousness. The term epilepsy refers to spontaneous recurrent seizures unrelated to fever. In other words, a patient who has a single nonfebrile seizure that does not recur over time would not merit the diagnosis of epilepsy. The ages of greatest risk for nonfebrile seizures are during infancy, childhood, and adolescence. The annual incidence rate from birth to 20 years of age is 0.56 per 1000; the cumulative risk of epilepsy during the first 2 decades of life is approximately 1%. The prevalence of epilepsy in the pediatric population is 4 to 6 cases per 1000 children.

**Classification and Description of Seizure Types**

Some may ask why it is necessary to classify epilepsy if the treatment and prognosis are similar for all children. There are primarily two forms of epilepsy characterized by either generalized seizures or a focal onset, and generalized and focal seizures respond predictably to some classes of anticonvulsants and not to others. The clinical appearance of a seizure may not indicate clearly whether the origin of the epileptiform discharge is focal or generalized. For example, a child may present with repetitive episodes of staring and unresponsiveness. Is this a generalized absence or a complex partial seizure? The proper classification will dictate the appropriate anticonvulsant. Finally, accurate classification of epilepsy permits the pediatrician to discuss the prognosis of the condition with the child and family. Most likely the child who has absence epilepsy will become seizure-free and not require medication as a teenager; focal seizures do not have the same favorable outcome.

The International Classification of Epileptic Seizures (ICES) was introduced in 1981 and is based primarily on the clinical description of the seizure and the associated changes on electroencephalogram (EEG). The majority of seizures can be classified according to the ICES nomenclature (Table I).

**PARTIAL SEIZURES**

Simple partial seizures (SPS) are associated most commonly with asynchronous clonic or tonic motor movements such as forced deviation of the head and eyes to one side. An SPS typically is short-lived, rarely persisting longer than 10 to 20 seconds, and the child remains conscious and is able to verbalize throughout it. The EEG characteristically shows unilateral spikes or sharp waves in the anterior temporal region, but the discharges may be bilateral; occasionally a multifocal spike pattern is recorded.

Complex partial seizures (CPS) initially may share the characteristic appearance of an SPS with or without an aura, followed by impairment of consciousness. Alternatively, CPS may begin with loss of consciousness. The average duration of a CPS is 1 to 2 minutes, which is significantly longer than an SPS or an absence seizure. Aura is common and signals the onset of a seizure in

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**ABBREVIATIONS**

BPV: Benign paroxysmal vertigo
CNS: Central nervous system
CPS: Complex partial seizure
CT: Computed tomography
EEG: Electroencephalogram
ICES: International Classification of Epileptic Seizures
MRI: Magnetic resonance imaging
PET: Positron emission tomography
SPECT: Single photon emission tomography
SPS: Simple partial seizure
Partial Seizures (focal onset seizures)
- Simple partial (consciousness retained)
  - With motor symptoms
  - With somatosensory or sensory symptoms
  - With autonomic symptoms
  - With psychic symptoms
- Complex partial (consciousness impaired)
  - Simple partial developing into a complex seizure
  - Consciousness impaired at onset
- Partial seizure with secondary generalization

Generalized Seizures
- Absence seizures
  - Typical
  - Atypical
- Myoclonic seizures
- Clonic seizures
- Tonic seizures
- Tonic-clonic seizures
- Atomic seizures

Unclassified Seizures


approximately 30% of children who have CPS, with the child complaining of epigastric discomfort, fear, or an unpleasant feeling at the outset (especially in the older child who can verbalize the nature of the aura). Automatisms are repetitive, stereotyped behaviors. These are the hallmark of CPS and occur in 50% to 75% of cases, particularly in the older child and adolescent. Automatisms follow the loss of consciousness and may remain evident in the postictal period, but unlike aura, the child is not aware of their presence. Automatisms common to the infant include lip smacking, chewing, repetitive swallowing, and excessive salivation; lip smacking, picking and pulling at clothing, constant rubbing of objects, or walking and running, often associated with a fearful expression, are observed more frequently in the child who has CPS. During the seizure, the epileptiform discharge may spread from a temporal lobe throughout the cortex, causing a generalized tonic-clonic convulsion (termed secondary generalization). The majority of children who have CPS have an abnormal EEG characterized by sharp waves or spike discharges in the anterior temporal or frontal lobe by multifocal spikes. Partial seizures are the most common form of epilepsy in children.

GENERALIZED SEIZURES
Simple (petit mal) absence seizures typically have their onset at 5 to 6 years of age and are characterized by brief (5 to 20 sec) lapses in consciousness, speech, or motor activity, sometimes associated with flickering of the eyelids. Absence seizures never are accompanied by an aura or a postictal period of drowsiness, but automatisms may be observed during the seizure. The automatisms usually consist of eye blinking or lip smacking. Hyperventilation for 3 to 4 minutes by the cooperative patient frequently induces a seizure. The EEG is characterized by 3 per second generalized spike and wave discharges.

Myoclonic seizures may occur in isolation or in association with other types of epilepsy, including tonic-clonic convulsions. Myoclonic seizures are characterized by brief, often repetitive symmetric muscle contractions with loss of normal body tone. Atonic seizures are difficult to differentiate from myoclonic seizures; in many cases they represent a prolonged myoclonic seizure. Atonic seizures typically cause the child to fall because of the sudden loss of postural tone.

Primary generalized tonic-clonic (formerly called grand mal) and tonic or clonic seizures are well known to most pediatricians. These seizures are characterized by sudden loss of consciousness and tonic-clonic, tonic, or clonic contractions. Tonic seizures are associated with intense muscle contraction and clonic seizures with rhythmic, usually symmetric jerking movements. The child may develop perioral cyanosis and lose bladder control. The seizure is followed by a 30 to 60 minute period of deep sleep and postictal headache.

SYNDRONOMIC CLASSIFICATION OF EPILEPSY
The major disadvantage of the ICES classification is its failure to recognize certain distinct epileptic syndromes that are age-related, are characterized by specific types of seizures, and have varying etiologies that differ significantly from causes of epilepsy in the adult patient population. A “syndromic” classification proposed in 1989 by the International League Against Epilepsy permits selection of an anticonvulsant that is most appropriate to treat the patient’s predominant seizure type. The primary drawback of this more sophisticated approach to diagnosis and treatment of a child’s epileptic syndrome is that at present, only approximately 50% of seizure disorders in children can be placed into a specific syndrome. For the purpose of this review, the clinical description, characteristic EEG patterns, treatment, and prognosis of five epileptic syndromes are outlined briefly in Table 2. These syndromes
include infantile spasms, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, benign childhood epilepsy with centrotemporal (rolandic) spikes, and juvenile myoclonic epilepsy (Janz syndrome).

**Etiology of Epilepsy**

Despite the advent of molecular diagnosis and new neuroimaging techniques, the etiology of most seizures in children remains unknown. The acute onset of seizures may result from cerebral trauma (head injury), CNS infection (meningitis, encephalitis), cerebrovascular diseases (infarction, arteriovenous malformation, hemorrhage, venous thrombosis), toxins (lead), brain tumor (cerebral or extracerebral), specific epilepsy syndromes (Table 2), genetic/heredi-
Epilepsy

Disorders commonly misdiagnosed as epilepsy include breathholding spells, gastroesophageal reflux, benign paroxysmal vertigo, and simple syncope.

Lundborg disease (chromosome 21q), and juvenile myoclonic epilepsy (chromosome 6p). The gene locus on chromosome 6 also may be responsible for other types of generalized epilepsy, including absence and generalized tonic-clonic seizures. Studies of large numbers of families that have other well-defined epilepsy syndromes likely will uncover additional epilepsy genes.

AGE AT ONSET
The age of presentation often provides a clue to the possible cause of epilepsy. Hypoxic-ischemic encephalopathy is the most common cause of seizures in the newborn, which characteristically are apparent within the first 24 hours. Children who have neonatal seizures following a hypoxic-ischemic insult are at significant risk to continue to have seizures (ie, epilepsy). Pyridoxine dependency may be the cause of seizures that begin shortly after birth, especially if they are associated with signs of fetal distress and particularly when there is a history of seizures in utero. Metabolic encephalopathies typically are associated with seizures in the newborn and usually are unresponsive to conventional anticonvulsants. The infant who has a urea cycle abnormality or a disorder of amino acid metabolism such as nonketotic hyperglycinemia may appear normal at birth, but within a few days will lose interest in feeding and sucking, followed by lethargy proceeding to coma and seizures, which often are of the myoclonic variety. Disorders of mitochondria, such as Leigh disease and pyruvate dehydrogenase deficiency, often present during infancy with repetitive seizures. The anoxic and metabolic encephalopathies that are associated with seizures will not be discussed further; several excellent reviews are included in the reading list.

STRUCTURAL ABNORMALITIES AND NEURONAL MIGRATION
With the advent of modern imaging technology, including magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET), it has become evident that structural abnormalities of the brain and congenital disorders of neuronal migration play an important role in the causation of epilepsy. The migrational abnormality may be severe and generalized, as seen in the child who has lissencephaly, which is characterized by a smooth brain due to a lack of gyri and a structure equivalent to a 12-week fetus. On the other hand, discrete collections of aberrant neurons visible by MRI imaging may be the cause of focal epilepsy in an otherwise normal child. A small number of children who have generalized infantile spasms have been found by EEG, MRI, SPECT, and PET scanning to have focal nests of dislocated neurons. In these cases, surgical excision of the abnormal cortex may result in complete seizure control.

FEBRILE SEIZURES
There is strong evidence that simple febrile seizures are not a cause of epilepsy, but whether a prolonged febrile seizure, especially during infancy, may cause mesial temporal sclerosis, thereby producing epilepsy at a later age, is still controversial. The cause of epilepsy in a cognitively and neurologically normal child has not been well defined; additional studies in these children may uncover a genetic basis.

Diagnosis
A presumptive diagnosis of epilepsy generally is made from a history of spontaneous recurrent seizures and findings on the physical examination because it is unlikely that the child will have a seizure in the presence of the physician. In response to careful questioning, the parent usually can give a good account of the seizure and whether it is generalized or focal in onset. The child also should participate in history taking because the existence of aura, which signifies a focal onset, may not be known to the parents. Certain seizures, such as absence or pseudo-seizures, may be provoked in the clinical setting by hyperventilation or the power of suggestion. If the history and description of seizures remain unclear, the parent can videotape seizures for later review by the pediatrician. Generally, if a diagnosis of epilepsy is in doubt following the examination and an EEG, it is in the child’s best interest to watch and wait before initiating specific treatment. It is possible that a condition mimicking epilepsy will become apparent during the period of observation.
child becomes cyanotic (occasionally pallid) and during the succeeding 30 to 60 seconds may have several generalized tonic-clonic movements before consciousness returns. The child is lethargic and sleepy for a brief period following the event. Gastroesophageal reflux may cause laryngospasm, bradycardia, and apneic episodes in an infant, which may be confused with a seizure disorder. Prompt management of the reflux usually brings the apnea under control.

Benign paroxysmal vertigo (BPV) often is confused with epilepsy. BPV causes the normal toddler to stagger or fall suddenly and to become pale and frightened. Some children will vomit during the episode, and all children will become dysarthric and complain of vertigo if they are able to verbalize. About 25% of children will have nystagmus during the attack. Although episodes of BPV usually are brief, persisting for 1 to 2 minutes, they may recur repetitively throughout the day.

Simple syncope (fainting) is common in the adolescent and adult but is unusual in a child younger than 10 years of age. Tilt-table testing is a useful method to distinguish simple syncope from a seizure when the diagnosis is uncertain.

Two types of syncope or loss of consciousness that begin during childhood may be confused with epilepsy and pose a significant hazard to the child. Cough syncope often is associated with poorly controlled asthma. These children develop cough paroxysms a few hours after falling asleep. The paroxysms may be so prolonged and persistent that the child loses consciousness and control of the bladder sphincter. There often are generalized tonic-clonic movements during the period of unconsciousness. The child has no recollection of these events the following morning. The prolonged QT syndrome results from an abnormality of myocardial function due to a familial or acquired insult, which may result in ventricular arrhythmias leading to sudden death. Children who have the prolonged QT syndrome are especially prone to cardiac arrhythmias during exercise or periods of anxiety or fear.

It is vital not to confuse this condition with simple syncope or epilepsy because genetic counseling, teaching the parents cardiopulmonary resuscitation, or introducing specific drug therapy aimed at preventing the arrhythmia (eg, beta blockers) may be life-saving.

Night terrors are common, especially in boys 4 to 6 years of age, and sometimes may be confused with epilepsy. They typically develop during the early stages of sleep and are characterized by the sudden onset of crying or screaming, uncontrollable flailing of the extremities, unintelligible speech, dilated pupils, and drooling. A few minutes later the child returns to sleep and has no recollection of the event.

The episodic dyscontrol syndrome (rage attacks) is a behavioral disorder observed primarily in boys ages 6 to 12 years. The rage attack always is provoked by a confrontation with a student, friend, or more likely a parent, usually the mother. Following the precipitating event, the child simply loses control, lashing out at the parent; scratching, biting, or physically injuring the person; and sometimes threatening the individual with a knife or weapon. There usually is profanity and verbal threats, but no loss of consciousness. At the conclusion of the episode, the child usually is remorseful. In my experience, the largest number of referrals are initiated by child psychiatrists who wish to exclude CPS as a possible etiology for the severe behavioral outbursts observed in these children.

Masturbation may mimic a seizure disorder. This behavior is seen most frequently in 2- to 4-year-old girls. In the recumbent position, the child develops repetitive rhythmic copulatory movements accompanied by a staring appearance, perspiration, plethoric facies, and unresponsive-ness to the parents’ or siblings’ voices.

Tics are involuntary, spasmodic, nonrhythmic, repetitive movements. Unlike seizures, tics are stereotypic logic findings observed during a seizure, such as unresponsive dilated pupils and extensor plantar responses. The eyelids may be closed firmly, and the patient resists eye opening by the examiner during a pseudoseizure. Because a significant number of children who have pseudoseizures also have epilepsy, the presence of epilepsy does not exclude the diagnosis. A useful rule of thumb is that urinary or fecal incontinence during the ictal event excludes the diagnosis of pseudoseizures. Adolescent girls subjected to incest or sexual abuse may present with pseudoseizures. The pediatrician must consider initiating a comprehensive evaluation to exclude sexual abuse for all adolescent girls who have pseudoseizures.

A routine interictal EEG will show an epileptiform abnormality in only about 60% of patients.

EEG AND NEUROIMAGING STUDIES

The EEG is a useful adjunct to the history and physical examination in establishing the diagnosis of epilepsy, but a routine interictal (between seizures) EEG will show
an epileptiform abnormality in only approximately 60% of patients. EEG abnormalities are more likely to be recorded in the infant or child who has epilepsy than in the adolescent or adult who has epilepsy. Various procedures are employed during the EEG in an attempt to activate a seizure discharge in a child suspected of having epilepsy, including eye closure, hyperventilation, photic stimulation, and in specific circumstances, sleep deprivation and special electrode placement (eg, zymographic leads). Prolonged EEG monitoring with simultaneous closed-circuit video recording is used in specific circumstances. For example, prolonged recording is useful for identifying ictal seizures that rarely are captured during routine EEG testing. Furthermore, prolonged EEG recording is particularly helpful in determining the location and frequency of seizure discharges while simultaneously visualizing and recording changes in levels of consciousness and the presence of clinical signs, which is critical for proper classification of the seizure disorder. Detailed localization and frequency of the seizure focus is essential for choosing appropriate candidates for epilepsy surgery. Finally, prolonged EEG recording is the “gold standard” test for investigating a patient who has suspected pseudoseizures.

Unfortunately, the routine EEG often is not used appropriately. It cannot be used reliably to determine the appropriate duration of anticonvulsant therapy or to explain a lack of response to therapy. The EEG does provide essential information in at least four situations: to support a diagnosis by typical EEG changes during the recording (eg, benign childhood epilepsy with centrotemporal spikes or absence epilepsy); to differentiate seizure disorders with similar clinical characteristics (eg, absence versus CPS); to detect potential structural brain lesions (focal slow-wave abnormalities); and to identify patients who have pseudoseizures.

Computed tomography (CT) is of little use in the evaluation of a child who has epilepsy, except in special circumstances such as investigation of a child suspected of having congenital Cytomegalovirus infection characterized by periventricular calcifications or tuberous sclerosis typified by calcified tubers in the subependymal layer. CT studies of children who have epilepsy have shown an abnormality in approximately 30% of cases, consisting primarily of cortical atrophy or dilated ventricles; this provides little useful information for clinical management.

MRI is gaining increasing importance in the study of children who have epilepsy, especially in examination of temporal lobe and hippocampal atrophy and sclerosis in patients resistant to anticonvulsant therapy. The use of MRI should be reserved for investigating all children who present with complex partial seizures, those who have a focal neurologic deficit (either static or postictal), those who present with complex seizures of increasing frequency or severity regardless of type, and all adolescents who have a first seizure.

Management
The initial step in the management of a child who is suspected of having epilepsy is to ensure that the paroxysmal event was, in fact, a seizure. A thorough history and examination coupled with appropriate studies and observation should distinguish nonepileptic events from seizures, as discussed previously.

Anticonvulsant withdrawal should be considered after a 2-year period of complete seizure control, with the weaning process occurring over a 4- to 6-month period.

Therapeutic Monitoring and Routine Screening
The amount of attention that should be given to the standard therapeutic ranges of anticonvulsants in the management of childhood epilepsy is very controversial (see Table 3). Some children achieve seizure control with subtherapeutic serum drug levels (eg, carbamazepine); for others, the seizures do not come under control until serum drug levels above the published range are reached (eg, valproic acid). Thus, if standard therapeutic serum levels are used as the only benchmark, children will be overtreated or undertreated routinely. There are specific periods when therapeutic drug monitoring is indicated: 1) At the initiation of therapy to ensure that the
therapeutic range is achieved, 2) During times of accelerated growth, and 3) If the seizures are out of control or the child is toxic. In general, the patient’s response to treatment is more important than the serum concentration of the drug.

I also recommend routine drug monitoring in the following clinical situations: 1) Children who undergo a change in seizure type; 2) Patients who continue to have seizures in spite of an adequate drug dose based on weight and age; 3) Patients who have hepatic or renal disease; 4) Children treated with phenytoin; 5) Patients receiving multiple drugs (polytherapy), especially valproic acid, lamotrigine, and phenobarbital, because drug interactions are common; 6) Children who have mental and physical handicaps in whom drug toxicity may be difficult to evaluate; and 7) Patients and families who are noncompliant with the drug regimen.

Adverse reactions to anticonvulsant drugs are common and on rare occasion may be life-threatening. Most serious adverse reactions occur

### TABLE 3. Common Anticonvulsant Drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SEIZURE TYPE</th>
<th>ORAL DOSE</th>
<th>THERAPEUTIC SERUM LEVEL</th>
<th>SIDE EFFECTS AND TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>µg/mL</td>
<td>µmol/L</td>
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<tr>
<td>ACTH</td>
<td>Infantile spasms</td>
<td>20 U IM/24 h for 2 wk. If no response, increase to 30 U and then 40 U IM/24 h for an additional wk</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Partial epilepsy</td>
<td>Begin 10 mg/kg per 24 h. Increase by 5 mg/kg per 24 h every wk to 20–30 mg/kg per 24 h in 2 or 3 divided doses</td>
<td>4–12</td>
<td>17–50</td>
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<tr>
<td></td>
<td>Tonic-clonic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Clonazepam</td>
<td>Myoclonic</td>
<td>Begin 0.05 mg/kg per 24 h. Increase by 0.05 mg/kg per wk. Maximum, 0.2 mg/kg per 24 h in 2 or 3 divided doses</td>
<td>6.3–56.8</td>
<td>0.02–0.18</td>
</tr>
<tr>
<td></td>
<td>Infantile spasms</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Absence</td>
<td></td>
<td></td>
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<tr>
<td>Ethosuximide</td>
<td>Absence</td>
<td>Begin 10 to 20 mg/kg per 24 h in 2 divided doses; may be increased to 50 mg/kg per 24 h</td>
<td>40–160</td>
<td>280–710</td>
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<tr>
<td></td>
<td>Myoclonic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin (add-on therapy)</td>
<td>Partial epilepsy</td>
<td>Begin 300 mg/24 h. Increase by 300 mg/24 h every 3 to 5 days. Maximum 900 to 1200 mg/24 h in 3 equally divided doses</td>
<td>&lt;2</td>
<td>&lt;11.7</td>
</tr>
<tr>
<td></td>
<td>Tonic-clonic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lamotrigine (add-on therapy)</td>
<td>Partial epilepsy</td>
<td>Begin 2 mg/kg per 24 h in 2 equal doses. Increase to maintenance dose of 5 to 15 mg/kg per 24 h. Lower doses begin 0.5 mg/kg per 24 h to maintenance of 1 to 5 mg/kg per 24 h if used with valproic acid</td>
<td>1–4</td>
<td>4–39</td>
</tr>
<tr>
<td></td>
<td>Tonic-clonic</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Lennox-Gastaut</td>
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during the initial 1 to 3 months of therapy and are more prominent when specific risks are present. For example, severe hepatotoxicity in association with valproic acid therapy is more likely to occur in the developmentally delayed or neurologically abnormal child younger than 2 years of age who is being treated with multiple anticonvulsants. The risk is even greater if the infant has an underlying metabolic disorder, particularly involving mitochondrial function. If the cause of the child’s seizure disorder is unknown, screening for a metabolic disorder (eg, blood gases, serum lactate and pyruvate, carnitine, ammonia, amino acids, and urinary organic acids) should be under-taken prior to the introduction of valproic acid.

Routine screening with liver function tests and a complete blood count does not necessarily select patients destined to develop a serious adverse drug reaction such as aplastic anemia, hepatotoxicity, or Stevens-Johnson syndrome. In many cases the drug complication becomes apparent clinically prior to changes in blood test results. Thus, careful clinical monitoring of the patient, especially during the initial phase of treatment, is mandatory to identify early adverse reactions.

### DRUG INTERACTIONS
Anticonvulsants may induce or inhibit enzyme production or they may displace another anticonvulsant from a shared plasma protein-binding site. Several anticonvulsants are capable of enzyme induction, including carbamazepine, primidone, phenytoin, and phenobarbital. When these drugs are used together, they may lower the plasma levels of each other by increasing the rate of metabolism. Conversely, enzyme inhibition tends to increase plasma levels by decreasing the rate of metabolism. An important example of this phenomenon is the potential for carbamazepine toxicity when erythromycin also is prescribed. Erythromycin inhibits microsomal enzyme systems, which results in decreased clearance of carbamazepine. Phenytoin and phenobarbital may be displaced from plasma protein-binding sites by valproic acid, which may lead to toxic serum levels that can be adjusted by lowering the dose of valproic acid. Valproic acid also reduces the plasma clearance and prolongs the

### TABLE 3. continued

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SEIZURE TYPE</th>
<th>ORAL DOSE</th>
<th>THERAPEUTIC SERUM LEVEL</th>
<th>SIDE EFFECTS AND TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>µg/mL</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Tonic-clonic</td>
<td>3 to 5 mg/kg per 24 h in 1 or 2 divided doses</td>
<td>15–40</td>
<td>65–170</td>
</tr>
<tr>
<td>Partial epilepsy</td>
<td></td>
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</tr>
<tr>
<td>Phenobarbital</td>
<td>Partial epilepsy</td>
<td>5 to 6 mg/kg per 24 h in 2 divided doses</td>
<td>10–20</td>
<td>40–80</td>
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<tr>
<td>Primidone</td>
<td>Tonic-clonic</td>
<td>Begin 50 mg/24 h in two divided doses. Gradually increase to 150 to 500 mg/24 h divided into 3 equal doses</td>
<td>5–12</td>
<td>25–55</td>
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<tr>
<td>Partial epilepsy</td>
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<tr>
<td>Sodium valproate</td>
<td>Tonic-clonic</td>
<td>Begin 10 mg/kg per 24 h. Increase by 5 to 10 mg/kg per wk. Usual dose, 20 to 60 mg/kg per 24 h in 2 or 3 divided doses</td>
<td>50–100</td>
<td>350–700</td>
</tr>
<tr>
<td>Absence</td>
<td></td>
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<tr>
<td>Myoclonic</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Partial epilepsy</td>
<td>Unclassified</td>
<td>Begin 30 to 40 mg/kg per 24 h. Increase by 10 mg/kg per wk. Maximum, 80 to 100 mg/kg per 24 h in 2 equal doses</td>
<td>1.4–14</td>
<td>10.8–108</td>
</tr>
<tr>
<td>Vigabatrin (add-on therapy; not yet available in US)</td>
<td>Partial epilepsy</td>
<td>Begin 30 to 40 mg/kg per 24 h. Increase by 10 mg/kg per wk. Maximum, 80 to 100 mg/kg per 24 h in 2 equal doses</td>
<td>1.4–14</td>
<td>10.8–108</td>
</tr>
</tbody>
</table>
half-life of lamotrigine. It is not known whether this interaction explains the increased incidence of severe skin rashes and Stevens-Johnson syndrome when valproic acid and lamotrigine are used simultaneously.

**BEHAVIORAL AND COGNITIVE SIDE EFFECTS**

Each anticonvulsant drug can cause unwanted behavioral and cognitive side effects in children. What often is not appreciated is that up to 30% of untreated children who have epilepsy experience behavioral problems, perhaps in part as a psychological reaction to the chronic condition or to dysfunction of the CNS. Furthermore, intellectual impairment has been well-described in children who have epilepsy. It often is difficult to determine whether behavior changes or poor academic performance by a child who has epilepsy is the result of the medication, the underlying seizure disorder, or both. Often the behavioral or performance problems are subtle, and they are recognized by parents or the teacher only after discontinuation of the anticonvulsant.

Phenobarbital causes behavioral side effects in up to 50% of children, including personality change, irritability, fitful sleep, hyperactivity, short attention span, and depression. Many of the unwanted symptoms become less apparent when the dose is decreased. Because of the high frequency of side effects associated with phenobarbital, this agent no longer is the drug of choice in the treatment of childhood epilepsy. In decreasing frequency, the following drugs also may cause similar behavioral problems—ACTH, benzodiazepines, carbamazepine, phenytoin, and primidone. Valproic acid is the least likely to affect a child’s behavior adversely. Valproic acid also has little untoward influence on a child’s cognitive performance, although any anticonvulsant may produce unwanted behavioral side effects.

If the child develops an adverse behavioral change following initiation of anticonvulsant therapy, the pediatrician has several options, including lowering the dose or if the problem persists, substituting another anticonvulsant for the offending drug. This situation also affords an opportunity to reassess the need for an antiepileptic drug. Follow-up should include an assessment of the child’s behavior and school performance on every visit. If academic or behavioral problems continue after drug readjustment or substitution, the child must be referred for a comprehensive evaluation to assess learning and cognitive parameters; plans also must be established for appropriate remediation.

**ANTICONVULSANT WITHDRAWAL**

If a child’s seizures are completely controlled for a period of approximately 2 years, consideration should be given to weaning from the anticonvulsant, particularly if the child has no risk factors for seizures. The most prominent risk factors associated with recurrence of seizures include developmental delay or child receiving monotherapy. Of those children who are seizure-free for 2 years and who have no risk factors, 70% to 75% will remain seizure-free without anticonvulsants. The most vulnerable time for seizure recurrence is the initial 6 months following drug withdrawal. If seizures recur, the child once again is placed on the drug that initially provided seizure control for at least 2 years. If the seizures reappear following a second drug withdrawal, life-long anticonvulsant therapy may be required.

**THE KETOGENIC DIET**

The ketogenic diet was used frequently for the treatment of intractable epilepsy before the discovery of the newer antiepileptics— carbamazepine, the benzodiazepines, and valproic acid. Interest has been renewed in this high-fat diet by tele-

**Children should not bathe or swim unattended, although children should be encouraged to participate in all activities as long as appropriate protective equipment is used.**
seizure control.

**SURGERY**

Surgery is gaining increasing popularity as a method of treating children who have focal seizures unresponsive to anticonvulsant therapy. The assessment of children for possible surgery must be conducted in a tertiary center by a skilled pediatric epileptologist in a multidisciplinary setting. Following routine EEGs, prolonged EEG recording with video monitoring is imperative to localize the site(s) and identify the frequency of epileptogenic discharges. Many centers use subdural electrodes to define the extent of the epileptogenic activity more accurately. These studies often are accomplished by decreasing or discontinuing the anticonvulsant drugs to promote frequent seizures, which increases the reliability of locating the seizure focus.

In addition to the EEG studies, the child undergoes a series of other procedures to assist in localization of the seizure focus and identification of the dominant cerebral hemisphere, including neuropsychologic evaluation, the Wada test (intracarotid injection of amobarbital), SPECT, PET in some centers, and MRI studies. These studies may identify a lesion corresponding to the focal seizure abnormality, including a low-grade glioma, hamartoma, or evidence of mesial temporal sclerosis. The results of epilepsy surgery in children who have a localized area of epileptogenic activity associated with a structural lesion is excellent. Temporal lobe resection is the most common surgery performed in children and adults; corpus callosotomy, hemispherectomy, and nontemporal lobe resections are more common in the younger child who has intractable seizures. Further development of electrophysiologic monitoring and advances in neurosurgery will allow more children who have focal seizures unresponsive to anticonvulsant therapy to benefit from epilepsy surgery.

**Counseling**

Appropriate and timely counseling of the parents and child is at least as important as choosing the correct anticonvulsant. Parents and patients who comprehend the purpose and side effects of anticonvulsant drugs as well as their action are much more likely to be compliant and supportive. At the time of diagnosis, the family often is overwhelmed and does not know where to start. It is useful initially to review the causes of epilepsy and explain the need for an EEG and additional studies if warranted. This consultation also provides an opportunity to dispel various myths about epilepsy.

Subsequent visits should focus on factors that may exacerbate seizures, including a low-grade fever, undue stress, lack of sleep, and certain drugs such as methylphenidate and the phenothiazines. On occasion, anticonvulsants, particularly carbamazepine and phenytoin, may potentiate seizures. The physician should review first-aid measures that can be initiated at home if a seizure occurs. I recommend that the child not bathe or swim unattended because a seizure could result in drowning. However, the pediatrician should encourage participation in all activities, including contact sports if the patient desires, as long as appropriate protective equipment is used. Because adolescents who have epilepsy are primarily concerned about obtaining a driver’s license, the pediatrician should be aware of state laws governing driver’s licenses for people who have epilepsy. It is imperative that school teachers be made aware of children who have epilepsy because the children are at risk for learning disorders and require careful surveillance to identify situations in which special assistance is needed.

The diagnosis of epilepsy frequently affects the family negatively. The parents are frightened that their child might die during a seizure, develop brain damage as a consequence of recurrent seizures, or have significant irreversible side effects from the anticonvulsant. Many parents feel guilty and vulnerable, particularly if there is a family history of epilepsy. If their fears and questions are not addressed adequately, a parent may tend to isolate the child, which will cause greater anxiety and family discord. The pediatrician must respond to the psychosocial needs of such a family. Most patients benefit from reading material produced by the Epilepsy Foundation of America and by participating in parent meetings sponsored by local epilepsy organizations. Time should be set aside at each follow-up visit to address concerns relating to any academic, social, or behavioral problems. As the parents become more familiar with the many facets of epilepsy, their confidence will grow and ability to cope will improve.

Most children who have epilepsy are well-controlled on anticonvulsant medication with few if any side effects, have normal intelligence, and can be expected to lead normal lives. The pediatrician can play a pivotal role in ensuring that the child who has epilepsy reaches his or her highest potential.

**SUGGESTED READING**


Tennison M, Greenwood R, Lewis D, Thorn M. Discontinuing antiepileptic drugs in...

**SUGGESTED RESOURCES FOR PARENTS AND CAREGIVERS**

The Epilepsy Foundation of America
4351 Garden City
Landover, MD 20785
1-800-332-1000

The Epilepsy Foundation of America is an excellent resource for parents. Information is provided on a wide range of topics, including the use of medication, states that require physicians to report individuals who have epilepsy to the Department of Motor Vehicles, and a list of Epilepsy Centers within a specific region.

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**PIR QUIZ**

1. On the basis of history alone, the patient most likely to have a true seizure disorder is:
   A. A 2-year-old boy who has a generalized clonic-tonic seizure lasting 2 to 3 minutes associated with acute otitis.
   B. A 3-year-old girl who has blue spells and loss of consciousness seemingly precipitated by minor injury to the extremities.
   C. A 5-year-old boy who has recurrent episodes of inconsolable crying and screaming shortly after falling asleep.
   D. A 5-year-old girl who has several episodes lasting 15 to 20 seconds characterized by unexpected cessation of speech with blank facial expression.
   E. A 12-year-old girl who has 3- to 5-minute episodes of moaning cries, bizarre posturing associated with falling, but no injury.

2. A true statement about the child in whom anticonvulsant therapy is initiated is:
   A. Adverse clinical reactions generally are preceded by measurable abnormalities in blood counts and liver function tests.
   B. Erythromycin inhibits microsomal enzyme systems, leading to reduced serum clearance of carbamazepine.
   C. It is essential that the anticonvulsant drug level be maintained within the recommended therapeutic range.
   D. Serious adverse reactions to anticonvulsant drugs usually occur after 6 or more months of treatment.
   E. Sodium valproate increases metabolism of phenobarbital, with resultant subtherapeutic levels of the latter drug.

Match each of the following anticonvulsants with the most commonly reported significant adverse effects:

3. Carbamazepine.  
5. Phenobarbital.  
6. Phenytoin.  
7. Sodium valproate.
   A. Diplopia.  
   B. Drowsiness and drooling.  
   C. Hepatotoxicity.  
   D. Hyperactivity, short attention span, and depression.  
   E. Stevens-Johnson Syndrome.

8. The diagnosis of a clonic-tonic seizure disorder was made in an 8-year-old boy 6 months ago. He had weighed 5 lb at birth and was in an observational nursery for 5 days. He has had no further seizures following institution of phenobarbital therapy. Findings on neurologic examination are normal, and he performs well at the appropriate grade level. His parents wish to discontinue the anticonvulsant therapy because they plan to enter him in swimming lessons. The most correct statement in this circumstance is:
   A. At least 75% of children have a recurrence of seizures on discontinuation of anticonvulsant therapy.
   B. Complete freedom from seizures for 2 years is an indication for discontinuing treatment gradually.
   C. Following discontinuation of anticonvulsant therapy, the drugs should be restarted at the first evidence of a febrile illness.
   D. The treatment must be discontinued for the child to enter a swimming class.

9. In the initial and continuing counseling of parents regarding various aspects of a convulsive disorder in their child, it is most important for them to know that:
   A. Adolescents will not be able to obtain a driver’s license until treatment is discontinued.
   B. Children who have a seizure disorder should not consider participation in contact sports.
   D. Teachers generally have no need to be informed about the seizure disorder.
   E. The most vulnerable time for seizure recurrence is in the initial 6 months following discontinuation of therapy.
Nonfebrile Seizures
Robert H. A. Haslam
*Pediatrics in Review* 1997;18;39
DOI: 10.1542/pir.18-2-39

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