Epilepsy is a neurological disorder that is defined as at least 2 unprovoked seizures. A seizure is defined as synchronous activity of a population of neurons that may be associated with clinical manifestations. To most lay people, a seizure must involve generalized clonic activity. However, many patients have seizures that do not involve clonic activity, but instead may consist of recurrent feelings of a similar nature, or episodes of behavioral arrest that are associated with loss of memory. Epilepsy is commonly referred to as a seizure disorder, but seizures and their causes can vary greatly, prompting a term, “the epilepsies.” Seizure disorders are complex in their etiologies, presentations, and management, and the consequences of a seizure extend far beyond the moments of lost motor control or cognitive function. There are numerous antiseizure or antiepileptic drugs (AEDs) now available. These may have different mechanisms of action, pharmacokinetic profiles, and differing adverse effects. Pharmacotherapy is often long-term, perhaps lifelong, with important potential adverse reactions and side effects that must be taken into consideration for each individual patient.

Etiology and Epidemiology

Seizures are the result of repetitive, synchronous discharges of cortical neurons. An imbalance occurs between excitatory and inhibitory neurons, resulting in sudden onset of excitation. The clinical signs or symptoms of seizures depend on the location of the seizure focus (or foci)—ie, the neuroanatomic location where the neurons are discharging—and the extent to which the neuronal discharges spread across the cortex. For example, discharges in the visual cortex may give rise to positive visual phenomena such as flashing lights; other signs include sensory, autonomic, or motor manifestations (dis-
Seizures can result from any number of neurologic disorders. The lifetime likelihood of experiencing at least 1 epileptic seizure is about 9%, and the lifetime likelihood of being diagnosed as having epilepsy is almost 3%. However, the prevalence of epilepsy in the US population is only 0.8%. The incidence of seizures is bimodal, maximal in the first year of life and in patients 75 years and older, with the greatest prevalence of 1.5% in elderly patients.

**Classification of Epilepsy Syndromes**

The International League Against Epilepsy (ILAE) last updated their classification of the epilepsies in 1989, and these criteria are now used as standard practice. They are currently being updated but, overall, the epilepsies are broadly divided into 2 categories: generalized and partial-onset (or localization-related) seizures, of idiopathic or symptomatic processes. Partial-onset seizures begin in a focal area of the cerebral cortex, while generalized seizures occur simultaneously in both cerebral hemispheres. The proposed new classification is to replace the terms “partial-onset” and “localization-related” with “focal.” The Sidebar lists other types of seizure categories that are localization-related or generalized epilepsy. As with many other disorders, not all seizures fit cleanly into either of these 2 categories, so some are classified as special syndromes (eg, febrile seizures) and some remain unclassified. Each seizure type is classified by its clinical and electroencephalography (EEG) manifestations, and sometimes requires prolonged, continuous video-EEG monitoring to diagnose an epilepsy.

Partial-onset seizures are further classified into 3 categories: simple partial seizures (SPS), complex partial seizures (CPS), and secondarily generalized tonic-clonic seizures. SPS are seizures where awareness and the ability to remember are preserved. They are sometimes referred to as an “aura,” but they are seizures and may occur in isolation or precede a CPS. The experiences of SPS can be sensory, motor, autonomic, or psychic. An SPS generally lasts from a few seconds to a few minutes. If it lasts longer than 30 minutes, it is referred to as simple partial status epilepticus. Diagnosis can be difficult as scalp EEG changes may be seen in only 50% of patients with SPS, and it relies on repeated occurrence, progression to a CPS or secondarily generalized seizure, or response to an AED. None of these signs alone is diagnostic of SPS. Of note, some patients with epilepsy may also experience a premonitory phase, prior to the SPS (“aura”). This phase is characterized by feelings of heaviness, depression, irritability, or gastrointestinal upset. CPS are seizures during which the patient appears conscious, but awareness is impaired. Most patients do not remember the loss of memory and are unable to recall the seizure. They may, however, recall the aura (or SPS). CPS of temporal lobe onset are characterized by behavioral arrest and staring, followed by automatisms (ie, automated movements such as chewing, lip smacking, mumbling, fumbling or picking with the hands). Postictal (or postattack) confusion is also common. CPS usually last about 60 to 90 seconds, although general weakness, asthenia, and fatigue may continue for up to a day. They are typically diagnosed by clinical history, EEG, and neuroimaging studies.

A secondarily generalized seizure often begins with either an SPS or CPS, and then evolves into generalized tonic-clonic activity, which is the most frequently recognized manifestation of a “seizure” (ie, the rapid, jerking movements and body convulsions). It is con-

<table>
<thead>
<tr>
<th>ILAE Classification of Epilepsies</th>
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<tbody>
<tr>
<td><strong>Localization-related (or focal) seizures</strong></td>
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<tr>
<td>- Idiopathic</td>
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<tr>
<td>- Benign childhood epilepsy</td>
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<tr>
<td>- Symptomatic</td>
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<tr>
<td>- Chronic progressive epilepsy partialis continua</td>
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<td>- Temporal lobe</td>
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<td>- Extratemporal</td>
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<tr>
<td><strong>Generalized epilepsy</strong></td>
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<tr>
<td>- Idiopathic</td>
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<td>- Benign neonatal convulsions</td>
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<td>- Childhood absence epilepsy (pyknolepsy)</td>
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<td>- Juvenile myoclonic epilepsy</td>
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<tr>
<td>- Other</td>
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<tr>
<td>- Cryptogenic or symptomatic</td>
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<td>- Infantile spasms (West syndrome)</td>
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<td>- Early myoclonic encephalopathy</td>
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<td>- Lennox-Gastaut syndrome</td>
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<td>- Progressive myoclonic epilepsy</td>
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<tr>
<td><strong>Special syndromes</strong></td>
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<tr>
<td>- Febrile convulsions</td>
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<tr>
<td><strong>Unclassified</strong></td>
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sidered to be secondarily generalized, however, because it is preceded by the SPS. However, many patients with secondarily generalized seizures often do not remember the SPS, so it is difficult to differentiate this from a generalized seizure disorder.

Generalized-onset seizures are classified into 6 major categories: (1) absence seizures, (2) tonic seizures, (3) clonic seizures, (4) myoclonic seizures, (5) tonic-clonic seizures, and (6) atonic seizures.

Absence seizures are brief episodes (often less than 20 seconds) of impaired awareness with no “aura” or postictal confusion. They may have associated facial automatisms, such as repetitive blinking. Absence seizures often are precipitated by hyperventilation, and typically begin during childhood or adolescence but may persist into adulthood. They are often not recognized until they progress to generalized tonic-clonic seizures, or more subtly, as a sudden decrease in school performance or overall attention. There appears to be a significant genetic component to absence seizures.

Myoclonic seizures are characterized by the frequently recognized brief arrhythmic jerking motor movements. Myoclonic seizures last less than 1 second but often occur as clusters within a few minutes. If they evolve into a rhythmic jerking, it is defined as clonic seizures, which can include impaired awareness. Upper and lower extremities are often both involved. Tonic seizures are characterized by sudden extension or flexion of the head, trunk, or extremities, usually in relation to drowsiness (shortly after falling asleep or just after awakening). They last for several seconds and are often associated with other neurological abnormalities.

Tonic-clonic seizures are most commonly thought of as “epilepsy” and in the past were referred to as “grand mal seizures,” a mid-1800s French term. (Of note, some patients still use the terms “grand mal” [generalized tonic-clonic] and “petit mal” [for all other seizures, but most often CPS or absence seizures], but these arcane terms create more confusion than clarity in determining the type of seizure. The pharmacist is encouraged to educate the patient on the correct type of seizure he/she experiences.) Tonic-clonic seizures involve the tonic extensions described above along with the clonic movements (rhythmic jerking), as well as prolonged confusion after the episode. They may not have an aura or follow an SPS.

Atonic seizures manifest as an abrupt loss of postural tone, often resulting in falls and associated injuries. These types of seizures typically occur in people with neurological abnormalities.

Status epilepticus is currently defined as continuous seizure activity for 30 minutes or longer, or 2 or more seizures during a 30-minute period where the patient does not return to baseline between the seizures. It may be partial (simple or complex) or generalized (nonconvulsive or convulsive). It is associated with increased morbidity and mortality, which is often dependent upon the etiology. Patients with a history of status epilepticus or cluster seizures are at increased risk of having future episodes of status epilepticus.

**Classification Based on Etiology**

Seizures (both partial and generalized) are also classified based on their etiology: symptomatic, cryptogenic, or idiopathic. Symptomatic seizures have an identified etiology or lesion, such as a stroke, tumor, vascular malformation, or cortical dysgenesis. Cryptogenic seizures are thought to be symptomatic, but an etiology cannot be identified. Idiopathic (“a disorder unto itself”) are thought to be genetic forms of epilepsy, which most often manifest as a generalized epilepsy, but may be seen as a partial epilepsy. Patients with idiopathic epilepsies often have normal intelligence and the seizures may have a specific age of onset and in most cases a specific age of offset. The seizures are generally controlled with the appropriate choice of AED.

**Febrile Seizures**

Febrile seizures occur uniquely in children ages 6 months to 5 years, always in the setting of a febrile illness. They are the most common seizure disorder in childhood, occurring in 2% to 5% of children. Febrile seizures can be classified as simple (70%-75%), or complex (25%-30%). A simple febrile seizure is a single seizure that lasts less than 10 to 15 minutes. It occurs in an otherwise neurologically healthy child and the fever is not caused by an infection that affects the brain (ie, meningitis or encephalitis). The seizures are generalized clonic or generalized tonic-clonic. A complex febrile seizure is a seizure that is focal, lasts longer than 10 to 15 minutes, or has multiple seizures occurring during the febrile illness. Febrile status epilepticus is a seizure that lasts 30 minutes or longer, that occurs during a febrile illness in a child without a prior history of epilepsy. Although febrile seizures are associated with fever, their exact cause is not known, but a genetic predisposition is a strong contributor. Approximately 30% of children over 1 year of age who have a febrile seizure will have a second seizure. That risk increases to 50% if the first
seizure occurs before age 1. Complex febrile seizures also increase the risk for epilepsy later in life, with prevalence rates of 2.4% by age 25 (about twice the risk for the general population). Importantly, febrile seizures do not lower intelligence or increase mortality. The benefits of long-term or intermittent AED treatment do not outweigh the risks for this type of seizure, especially because there is no evidence to suggest that these drugs will be preventive for febrile seizures. In rare cases, rectal diazepam can be administered as a preventive with each fever. Antipyretics, however, are recommended, but they do not prevent simple febrile seizures.

**New Directions in Classification**

As mentioned previously, the ILAE is now considering a new classification scheme, which would categorize seizures based on 5 axes: ictal phenomenology, seizure type, syndrome, etiology, and impairment. This scheme serves more to standardize diagnosis of individual patients, rather than adjusting the current classification scheme to meet all clinical and research criteria.

**Consequences of Epilepsy: Overall Patient Health and Quality of Life**

Most patients with epilepsy are able to lead healthy, productive lives. However, this can only occur through good control of the disease and appropriate patient education and support. Unfortunately, roughly one third of patients do not enjoy seizure control, mostly due to medically refractory epilepsy, but in some cases due to problems with AED side effects.

Epilepsy does not often exist alone; several disorders are often comorbid with epilepsy including depression, anxiety, and migraine. An additional comorbidity in children is attention-deficit hyperactivity disorder. Psychiatric and behavioral comorbidities are believed to affect approximately 40% to 50% of children and adolescents with epilepsy. The prevalence of depression in epilepsy is much higher than in the general population, ranging from 20% to 55% in those with recurrent seizures, and from 3% to 9% in those with controlled seizures.

Evidence from studies of other chronic illnesses suggests that mood is an important factor in compliance; thus poor compliance begets poor seizure control, which begets further depression and anxiety—a vicious cycle. Major depression in epilepsy is associated with significantly decreased self-reported quality of life, increased disability and missed work, and increased medication and medical costs. Gilliam et al. have shown that depression or psychological distress may be the strongest predictors of health-related quality of life, even including seizure frequency and severity, employment, or driving status.

Not surprisingly, with the high rate of depression, people with epilepsy are at increased risk for suicide, both in attempts and completed suicides. The lifetime prevalence of suicide among those with epilepsy is 5% to 14.3% versus 1.1% to 1.2% for the general population. These rates increase to 6 to 25 times higher in those with temporal lobe epilepsy and even higher for those who have had epilepsy surgery.

Studies of mortality and hospitalization rates for patients with epilepsy are difficult to analyze in aggregate because of the differences in study design, definitions of epilepsy, and accuracy of diagnosis. However, a recent study of 564 patients followed for 15 years showed a decreased life expectancy of up to 10 years in those with symptomatic epilepsy and up to 2 years in those with idiopathic/cryptogenic epilepsy. Although many deaths in patients with epilepsy may be caused by a seizure (drowning, head injury, falls), as many as 10% of all deaths in patients with epilepsy may be unexplained, called sudden unexpected death in epilepsy (SUDEP).

Driving is one of the most prominent concerns of epilepsy patients, along with independence and ability to work. Persons with epilepsy are restricted from driving up to 12 months after diagnosis in 13 states; most other states require 6 months of prohibited driving. Given our reliance on the automobile for transportation in the United States, revocation of driving privileges causes significant limitation and social isolation. A dangerous precedent is now being recognized as a result. Some patients may not report epilepsy to their physician, in part because of the driving restrictions. In a cross-sectional study in the United Kingdom, 122 patients completed anonymous questionnaires about their health. About one sixth of the study participants reported seizures in the last year in the questionnaire but did not report them to their physician. Forty percent of patients who anonymously reported a seizure in the questionnaire held a driver’s license, but only one fourth of these admitted this to their physician.

Each seizure may inflict neurological damage to the brain and thus may have cumulative, long-term sequelae. We are now beginning to document cognitive decline in patients with each seizure, although it is very subtle and of slow onset. Differentiating the cognitive decline with seizure from that associated with AED use can be
difficult. In general, however, poor cognitive outcome is generally associated with an early onset, a long duration of the disease, poor seizure control, and lower education levels (low cerebral reserve). Thus, it is important to treat seizure disorders early, not only before any cognitive dysfunction sets in, but also to avoid another vicious cycle—of poorly controlled disease, low self-esteem, poor performance in school, and thus limited earning potential and career opportunities later in life.

CONCLUSION

Epilepsy can be a surprisingly difficult disorder to diagnose and classify, because of its many manifestations and causes. Nonetheless, once the correct diagnosis is made, there are numerous pharmacological and nonpharmacological therapeutic options that can be tailored to each patient. Seizure disorders have an enormous impact on a person’s and family’s quality of life. Even when they rarely occur, seizures can cause physical, psychological, and perhaps even cognitive injury. Thus, good seizure control is critical.

REFERENCES