**Epilepsy**

**I. OVERVIEW**

Epilepsy affects approximately 3 percent of individuals by the time they are 80 years old. About 10 percent of the population will have at least one seizure in their lifetime. Globally, epilepsy is the third most common neu- rologic disorder after cerebrovascular and Alzheimer disease. Epilepsy is not a single entity. Instead it is, an assortment of different seizure types and syndromes originating from several mechanisms that have in com- mon the sudden, excessive, and synchronous discharge of cerebral neu- rons. This abnormal electrical activity may result in a variety of events, including loss of consciousness, abnormal movements, atypical or odd behavior, and distorted perceptions that are of limited duration but recur if untreated. The site of origin of the abnormal neuronal firing determines the symptoms that are produced. For example, if the motor cortex is involved, the patient may experience abnormal movements or a general- ized convulsion. Seizures originating in the parietal or occipital lobe may include visual, auditory, and olfactory hallucinations. Medication or vagal nerve stimulator therapy is the most widely effective mode for the treat- ment of patients with epilepsy. It is expected that seizures can be con- trolled completely in approximately 70 to 80 percent percent of patients with one medication. It is estimated that approximately 10 to 15 percent of patients will require more than one drug, and perhaps about 10 per- cent may not achieve complete seizure control. A summary of antiseizure drugs is shown in Figure 15.1.

**II. IDIOPATHIC AND SYMPTOMATIC SEIZURES**

In most cases, epilepsy has no identifiable cause. Focal areas that are functionally abnormal may be triggered into activity by changes in physi- ologic factors, such as an alteration in blood gases, pH, electrolytes, and blood glucose level and changes in environmental factors, such as sleep deprivation, alcohol intake, and stress. The neuronal discharge in epilepsy results from the firing of a small population of neurons in some specific area of the brain that is referred to as the “primary focus.” Anatomically, this focal area may appear to be normal. However, advances in technolo- gy have improved the ability to detect abnormalities. Neuroimaging tech- niques, such as magnetic resonance imaging (MRI), positron-emission tomography (PET) scans, and single-photon-emission coherence tomog- raphy (SPECT) may identify areas of concern (Figure 15.2). Epilepsy can be labeled idiopathic if the etiology is unknown or symptomatic if it is secondary to an identifiable condition. Though multiple specific epilepsy syndromes that include symptoms other than seizures have been classi- fied, a discussion of these syndromes is beyond the scope of this chapte

1. **Idiopathic epilepsy**

When no specifi c anatomic cause for the seizure, such as trauma or neoplasm, is evident, a patient may be diagnosed with idiopathic or cryptogenic (primary) epilepsy. These seizures may result from an inherited abnormality in the central nervous system (CNS). Patients are treated chronically with antiseizure drugs or vagal nerve stimulation. Most cases of epilepsy are idiopathic.

1. **Symptomatic epilepsy**

A number of causes, such as illicit drug use, tumor, head injury, hypogly- cemia, meningeal infection, and the rapid withdrawal of alcohol from an alcoholic, can precipitate seizures. When two or more seizures occur, the patient may be diagnosed with symptomatic (secondary) epilepsy. Chronic treatment with antiseizure medications, vagal nerve stimula- tion, and surgery are all appropriate treatments and may be used alone or in combination. In some cases when the cause of a single seizure can be determined and corrected, therapy may not necessary. For example, a seizure that is caused by transient hypotension or is due to a drug reaction is not epilepsy and does not require chronic therapy. In other situations, antiseizure drugs may be given until the primary cause of the seizures can be corrected.

**III. CLASSIFICATION OF SEIZURES**

It is important to correctly classify seizures to determine appropriate treat- ment. Seizures have been categorized by site of origin, etiology, electro- physiologic correlation, and clinical presentation. The International League Against Epilepsy (ILAE) developed a nomenclature for describing seizures. This classifi cation is considered the standard way to describe seizures and epilepsy syndromes (Figure 15.3). Seizures have been classifi ed into two broad groups: partial (or focal), and generalized. A diagnosis may include classifying the seizure as partial or generalized epilepsy depending on the onset.

1. **Partial**

 Partial seizures involve only a portion of the brain, typically part of one lobe of one hemisphere. The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the elec- trical activity spreads to other neuron777777777777s in the brain. Consciousness is usually preserved. Partial seizures may progress to become generalized tonic-clonic seizures.

1**. Simple partial**: These seizures are caused by a group of hyper- active neurons exhibiting abnormal electrical activity, which are confi ned to a single locus in the brain. The electrical discharge does not spread, and the patient does not lose consciousness. The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the distur- bance. The patient may also show sensory distortions. This activity may spread. Simple partial seizures may occur at any age.

**2. Complex partial:** These seizures exhibit complex sensory hallucina- tions and mental distortion. Motor dysfunction may involve chew- ing movements, diarrhea, and/or urination. Consciousness is altered. Simple partial seizure activity may spread to become complex and then spread to a secondary generalized convulsion. Complex partial seizures may occur at any age.

**B. Generalized**

 Generalized seizures may begin locally and then progress to include abnormal electrical discharges throughout both hemispheres of the brain. Primary generalized seizures may be convulsive or nonconvul- sive, and the patient usually has an immediate loss of consciousness.

 **1. Tonic-clonic:** These seizures result in loss of consciousness, fol- lowed by tonic (continuous contraction) and clonic (rapid contrac- tion and relaxation) phases. The seizure may be followed by a period of confusion and exhaustion due to the depletion of glucose and energy stores.

2**. Absence:** These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond. The patient stares and exhibits rapid eye-blinking, which lasts for 3 to 5 seconds. An absence seizure has a very distinct three-per-second spike and wave discharge seen on electroencephalogram.

 **3. Myoclonic**: These seizures consist of short episodes of muscle con- tractions that may recur for several minutes. They generally occur after wakening and exhibit as brief jerks of the limbs. Myoclonic seizures occur at any age but usually begin around puberty or early adulthood.

 4**. Febrile seizures**: Young children may develop seizures with illness accompanied by high fever. This tendency may run in siblings. Febrile seizures consist of generalized tonic-clonic convulsions of short duration and do not necessarily lead to a diagnosis of epilepsy.

**5. Status epilepticus**: In status epilepticus, two or more seizures occur without recovery of full consciousness between them. These may be partial or primary generalized, convulsive or nonconvulsive. Status epilepticus is life-threatening and requires emergency treatment.

**C. Mechanism of action of antiepileptic drugs**

Drugs reduce seizures through such mechanisms as blocking voltage- gated channels (Na+ or Ca2+), enhancing inhibitory γ-aminobutyric acid (GABA)-ergic impulses, and interfering with excitatory glutamate transmission. Some antiepileptic drugs appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defi ned. Antiepilepsy drugs suppress seizures but do not “cure” or “prevent” epilepsy.

**IV. DRUG CHOICE**

Choice of drug treatment is based on the classifi cation of the seizures, patient-specifi c variables (for example, age, comorbid medical conditions, lifestyle, and personal preference), and characteristics of the drug (such as cost and interactions with other medications). For example, partial onset seizures are treated with a diff erent set of medications than primary gen- eralized seizures, although the list of eff ective agents overlaps. Several of the antiseizure drugs may be equally eff ective. The toxicity of the agent and characteristics of the patient are major considerations in drug selection and treatment plan. In newly diagnosed patients, monotherapy is instituted with a single agent until seizures are controlled or toxicity occurs (Figure 15.4). Compared to those receiving combination therapy, patients receiving monotherapy exhibit better adherence and fewer side eff ects. If seizures are not controlled with the fi rst drug, monotherapy with an alternate antiepi- leptic drug or drugs should be considered. Failing that, consider vagal nerve stimulation (Figure 15.5). Awareness of the antiepileptic drugs available and their mechanisms of action, pharmacokinetics, potential for drug–drug interactions, and adverse eff ects is essential for successful treatment of the patient. There will be patients who require a combination of medications to control their seizures.

**V. PRIMARY ANTIEPILEPTIC DRUGS**

During the past 20 years, the Food and Drug Administration (FDA) has approved many new antiepileptic drugs. Some of these agents seemed to show potential advantages over drugs approved prior to 1990 in terms of pharmacokinetics, tolerability, and reduced risk for drug–drug interac- tions. The list of drugs approved since 1990 includes felbamate, gabapen- tin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufin- amide, tiagabine, topiramate, vigabatrin, and zonisamide. These are labeled “second generation” when compared with older antiepileptics, such as car- bamazepine, divalproex, ethosuximide, phenobarbital, phenytoin, and valp- roic acid. However, several studies have failed to provide sufficient evidence that the second-generation drugs are significantly better than the older agents in terms of efficacy and lack of adverse effects. For that reason, the most commonly used antiepileptic drugs are described in alphabetic order, rather than attempting to rank them by efficacy. Figure 15.6 shows common adverse effects of the antiepileptic drugs. Those drugs with an increased risk of suicidal behavior and suicidal ideation require an FDA black box warning on the label.

1. **Benzodiazepines**

Benzodiazepines bind to GABA inhibitory receptors to reduce firing rate. Diazepam and lorazepam are most often used as an adjunctive therapy for myoclonic as well as for partial and generalized tonic-clonic seizures. Lorazepam (see p. 114) has a shorter pharmacokinetic half-life but stays in the brain longer than diazepam. Diazepam is available for rectal administration to avoid or interrupt prolonged generalized tonic- clonic seizures or clusters. Other benzodiazepines may be used in the treatment of various epilepsies but should be considered for use only after trials with monotherapy or combinations of most other medica- tions for treatment of seizures fail.

1. **Carbamazepine**

Carbamazepine [kar-ba-MAZ-a peen] reduces the propagation of abnormal impulses in the brain by blocking sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread. Carbamazepine is effective for treat- ment of partial seizures and, secondarily, generalized tonic-clonic sei- zures. It is also used to treat trigeminal neuralgia and bipolar disor- der. Carbamazepine is absorbed slowly and erratically following oral administration and may vary from generic to generic, resulting in large variations in serum concentrations of the drug. It induces its own drug metabolism and has an active metabolite. It is a substrate for CYP3A4 with minor metabolism by CYP1A2 and CYC2C8. The epoxide metabo- lite accounts for 25 percent of the dose, is active, and can be inhibited by drugs that inhibit UDP glucuronosyltransferase (UGT), leading to toxicity (Figure 15.7). Carbamazepine is an inducer of the isozyme fami- lies CYP1A2, CYP2C, and CYP3A and UGT enzymes, which may increase the clearance and reduce the efficacy of drugs that they metabolize. It is not as well tolerated by the elderly as are other available antiseizure medications. Hyponatremia may be noted in some patients, especially the elderly, and could indicate a need for change of therapy. A charac- teristic rash may develop early in therapy but may not require a change in treatment. Carbamazepine should not be prescribed for patients with absence seizures because it may cause an increase in seizures.

1. **Ethosuximide**

Ethosuximide [eth-oh-SUX-i-mide] reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels. It is effective in treating only primary generalized absence sei- zures (see Figure 15.5). Use of ethosuximide is limited because of this very narrow spectrum of activity.

1. **Felbamate**

Felbamate [FEL-ba-mate] has a broad spectrum of anticonvulsant action. The drug has multiple proposed mechanisms including 1) blocking voltage-dependent sodium channels, 2) competing with the glycine-coagonist binding site on the N-methyl-D-aspartate (NMDA) glu- tamate receptor, 3) blocking calcium channels, and 4) potentiating the action of GABA. It is an inhibitor of drugs metabolized by CYP2C19 and β-oxidation (Figure 15.7), and induces drugs metabolized by CYP3A4. It is reserved for use in refractory epilepsies (particularly Lennox-Gastaut syndrome) because of the risk of aplastic anemia (about 1:4000) and hepatic failure.

**E. Gabapentin**

Gabapentin [GA-ba-pen-tin] is an analog of GABA. However, it does not act at GABA receptors, and it neither enhances GABA actions nor is converted to GABA. Its precise mechanism of action is not known. It is approved as adjunct therapy for partial seizures and for treatment of postherpetic neuralgia. Gabapentin exhibits nonlinear pharmacokinet- ics (see p. 14) due to its uptake by a saturable transport system from the gut. Gabapentin does not bind to plasma proteins and is excreted unchanged through the kidneys. Reduced dosing is required in renal disease. Gabapentin has been shown to be well tolerated by the elderly population with partial seizures due to its relatively mild adverse effects. It may also be a good choice for the older patient because there are lim- ited or no reported associated pharmacokinetic drug interactions.

1. **Lacosamide**

Lacosamide [la-KOE-sa-mide] in vitro affects voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal mem- branes and inhibition of repetitive neuronal firing. Lacosamide binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein mainly expressed in the nervous system and involved in neuronal differ- entiation and control of axonal outgrowth. The role of CRMP-2 binding in seizure control is unknown. Lacosamide is approved for adjunctive treatment of partial seizures. In clinical trials, the drug caused euphoria similar to that produced by alprazolam and is labeled as a controlled substance (Schedule V). It is available in an injectable formulation. The most common adverse events that limit treatment include dizziness, headache, and fatigue.