1. **Lamotrigine**

Lamotrigine [la-MOE-tri-jeen] blocks sodium channels as well as high voltage–dependent calcium channels. Lamotrigine is effective in a wide variety of seizure types, including partial seizures, generalized seizures, and typical absence seizures and in the Lennox-Gastaut syndrome. It is approved for use in bipolar disorder as well. Lamotrigine is metabolized primarily to the N-2 glucuronide through the UGT pathway. The half-life of lamotrigine (24–35 hours) is decreased by enzyme-inducing drugs (for example, carbamazepine and phenytoin) and increased by greater than 50 percent with the addition of valproate. Lamotrigine dosages should be reduced when adding valproate to therapy unless the valproate is being added in a small dose to provide a boost to the lamotrigine serum concentration. Rapid titration to high serum concentrations of lamotrigine have been reported to cause a rash, which in some patients may progress to a serious, life-threatening reaction. Lamotrigine has also been shown to be well tolerated by the elderly population with partial seizures due to its relatively minor adverse effects.

1. **Levetiracetam**

Levetiracetam [lee-ve-tye-RA-se-tam] is approved for adjunct therapy of partial onset seizures, myoclonic seizures, and primary generalized ton- ic-clonic seizures in adults and children. The exact mechanism of anti- convulsant action is unknown. It demonstrates high affinity for a synap- tic vesicle protein (SV2A). In mice, this was associated with potent anti- seizure action. The drug is well absorbed orally and excreted in urine mostly (66 percent) unchanged. The drug does not interact with CYP or UGT metabolism systems. Side effects most often reported include diz- ziness, sleep disturbances, headache, and weakness.

1. **Oxcarbazepine**

Oxcarbazepine [ox-kar-BAY-zeh-peen] is a prodrug that is rapidly reduced to the 10-monohydroxy (MHD) metabolite responsible for its anticonvulsant activity. MHD blocks sodium channels, preventing the spread of the abnormal discharge. It is also thought to modulate calcium channels. It is approved for use in adults and children with par- tial onset seizures. Oxcarbazepine is a less potent inducer of CYP3A4 and UGT than carbamazepine. The adverse effects profile is similar to that of other antiepileptic drugs. It can cause nausea, vomiting, headache, and visual disturbances.

1. **Phenobarbital**

Phenobarbital [fee-noe-BAR-bih-tal] was synthesized in 1902 and brought to the market in 1912 by Bayer. Its primary mechanism of action is enhancing the inhibitory effects of GABA-mediated neurons (see p. 113). Phenobarbital in epilepsy should be used primarily in the treatment of status epilepticus.

1. **Phenytoin and fosphenytoin**

Phenytoin [FEN-i-toin] blocks voltage-gated sodium channels by selec- tively binding to the channel in the inactive state and slowing its rate of recovery. At very high concentrations, phenytoin can also block voltage- dependent calcium channels and interfere with the release of mono- aminergic neurotransmitters. Phenytoin is effective for treatment of par- tial seizures and generalized tonic-clonic seizures and in the treatment of status epilepticus (see Figure 15.5). The drug is 90 percent bound to plasma albumin. Phenytoin induces drugs metabolized by the CYP2C and CYP3A families and the UGT enzyme system. Phenytoin exhibits saturable enzyme metabolism at a low serum concentration. Therefore, knowledge of zero-order pharmacokinetics and population parameters is important for dosing adjustment. Small increases in a daily dose can produce large increases in the plasma concentration, resulting in drug- induced toxicity (Figure 15.8). Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia. The elderly are highly susceptible to this eff ect. Gingival hyperplasia may cause the gums to grow over the teeth (Figure 5.9). Long-term use may lead to development of peripheral neuropathies and osteoporo- sis. Although phenytoin is the drug used most commonly worldwide for epilepsy due to its low cost per tablet, the cost of therapy may be much higher when the potential for serious toxicity and adverse eff ects is weighed. Fosphenytoin [FOS-phen-i-toin] is a prodrug and is rapidly convert- ed to phenytoin in the blood, reaching high levels within minutes. Fosphenytoin may also be administered intramuscularly (IM). However, phenytoin sodium should never be given IM because it can cause tissue damage and necrosis. Fosphenytoin is the drug of choice and standard of care for IV and IM administration. Because of sound-alike and looka- like trade names, there is a risk for prescribing errors. The trade name of fosphenytoin is Cerebyx®, which is easily confused with Celebrex®, the cyclooxygenase-2 inhibitor, and Celexa®, the antidepressant.

1. **Pregabalin**

Pregabalin [pree-GABA-lin] binds to the α2-δ site, an auxiliary subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release. The exact role this plays in treatment is not known, but the drug has proven eff ects on partial onset seizures, neu- ropathic pain associated with diabetic peripheral neuropathy, posther- petic neuralgia, and fi bromyalgia. More than 90 percent of pregabalin is eliminated renally, with no indication of CYP involvement. Drowsiness, blurred vision, weight gain, and peripheral edema have been reported.

1. **Rufi namide**

Rufi namide [roo-FIN-a-mide] in vitro acts at the sodium channels. It is approved for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children over age 4 years and in adults. Rufi namide is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 enzymes. Food increases absorption and peak serum concentrations. Serum concentrations of rufi namide are aff ected by other antiseizure medications. It is induced by carbamazepine and phenytoin and inhib- ited when given with valproate. Women taking birth control tablets should be counseled that they may not be eff ective when used concur- rently with rufi namide. Adverse eff ects include the potential for short- ened QT intervals. Patients with familial short QT syndrome should not be treated with rufi namide.

1. **Tiagabine**

Tiagabine [ty-AG-a-been] blocks GABA uptake into presynaptic neu- rons, permitting more GABA to be available for receptor binding, and therefore, to enhanced inhibitory activity. Tiagabine is eff ective in decreasing the number of seizures in patients with partial onset epilep- sy. Binding to albumin and α1-acid glycoprotein is greater than 95 per- cent. Metabolism is mainly completed by the CYP3A family of enzymes. Adverse eff ects include fatigue, dizziness, and gastrointestinal upset. There is some indication in postmarketing surveillance that seizures have occurred in patients using tiagabine who did not have epilepsy. Tiagabine has not been approved for and should not be used for any other indication.

1. **Topiramate**

Topiramate [toe-PEER-a-mate] has several actions that are believed to contribute to its broad spectrum of antiseizure activity. Topiramate blocks voltage-dependent sodium channels, and it has been shown to increase the frequency of chloride channel opening by binding to the GABAA receptor. High-voltage calcium currents (L type) are reduced by topiramate. It is a carbonic anhydrase inhibitor and may act at gluta- mate (NMDA) sites. Topiramate is effective and approved for use in par- tial and primary generalized epilepsy. It is also approved for treatment of migraine. Topiramate is eliminated renally, but it also has inactive metabolites. It inhibits CYP2C19 and is induced by phenytoin and car- bamazepine. Lamotrigine is reported to cause an increase in topiramate concentration. Coadministration of topiramate reduces ethinyl estradiol. Therefore, women taking the drug should be counseled to use addi- tional methods of birth control. Adverse effects include somnolence, weight loss, and paresthesias. Renal stones are reported to occur at a higher incidence than in a nontreated population. Glaucoma, oligo- hidrosis, and hyperthermia have also been reported. The latter are spe- cifically related to the carbonic anhydrase activity.

1. **Valproic acid and divalproex**

Valproic acid is available as a free acid. Divalproex sodium is a combi- nation of sodium valproate and valproic acid that is converted to val- proate when it reaches the gastrointestinal tract. It was developed to improve gastrointestinal tolerance of valproic acid. All of the available salt forms are equivalent in efficacy (valproic acid and valproate sodium). Commercial products are available in multiple-salt dosage forms and extended-release formulations. Therefore, the risk for medication errors is high, and it is essential to be familiar with all preparations. Possible mechanisms of action include sodium channel blockade, blockade of GABA transaminase, and action at the T-type calcium channels. These varied mechanisms provide a broad spectrum of activity against sei- zures. is the drugs are effective for the treatment of partial and primary generalized epilepsies. Valproate inhibits metabolism of the CYP2C9, UGT, and epoxide hydrolase systems (see Figure 15.7). Valproate is bound to albumin (greater than 90 percent), which can cause signifi- cant interactions with other highly protein-bound drugs. Rare hepatic toxicity may cause a rise in hepatic enzymes in plasma, which should be monitored frequently. Teratogenicity is also of great concern. Therefore, all women of childbearing age should be placed on other therapies and counseled about the potential for birth defects, including cognitive (Figure 15.10) and behavioral abnormalities and neural tube defects.

1. **Vigabatrin**

Vigabatrin [vyeGA-ba-trin] acts as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T). GABA-T is the enzyme responsible for metabolism of GABA. Vigabatrin is associated with adverse effects resulting in visual field loss ranging from mild to severe in 30 percent or more of patients. Vigabatrin is only available through pharmacies that participate in the SHARE program (1-888-45-SHARE). Physicians must be registered with SHARE to prescribe vigabatrin.

1. **Zonisamide**

Zonisamide [zoe-NIS-a-mide] is a sulfonamide derivative that has a broad spectrum of action. The compound has multiple effects on neuronal systems thought to be involved in seizure generation. These include blockade of both voltage-gated sodium channels and T-type calcium currents. It has a limited amount of carbonic anhydrase activ- ity. Cross reactivity with other sulfonamides should be reviewed. Its use should be monitored in patients with reported allergies. Zonisamide is approved for use in patients with partial epilepsy. It is metabolized by the CYP3A4 isozyme and may, to a lesser extent, be affected by CYP3A5 and CYP2C19. In addition to typical CNS adverse effects, zonisamide may cause kidney stones. Oligohidrosis has been reported, and patients should be monitored for increased body temperature and decreased sweating.

**VI. VAGAL NERVE STIMULATION**

Vagal nerve stimulation (VNS) requires surgical implant of a small pulse gen- erator with a battery and a lead wire for stimulus (Figure 15.11). The device is implanted and its lead wires wrapped around the patient’s vagal nerve. This treatment was approved in 1997. The device is also approved for treatment of depression. The mechanism of action is unknown. Because it has diffuse involvement with neuronal circuits, there are a variety of mechanisms by which it may exert its effect on seizure control. VNS has been effective in treatment of partial onset seizures and has enabled reduction of drug ther- apy in some cases. It is an alternative for patients whose conditions have been refractory to multiple drugs and in those who are sensitive to the many adverse effects of antiseizure drugs and those who have difficulty adhering to medication schedules. However, VNS is a costly and invasive procedure.

**VII. DEEP BRAIN STIMULATION**

Deep brain stimulation (DBS) therapy uses a pacemaker-like device to deliv- er targeted electrical stimulation to the anterior nucleus of the thalamus. The therapy is FDA approved with conditions for adjunctive treatment for partial-onset seizures in adults with medically refractory epilepsy. DBS is also FDA approved for treatment of advanced Parkinson disease and essen- tial tremor.

**VIII. EPILEPSY IN PREGNANCY**

Women with epilepsy are often very concerned about pregnancy and what effect the medications might have on fetal development. Planning is the most important component. All women considering pregnancy should be on high doses of folic acid prior to conception. Divalproex and barbiturates should be avoided. Those women already on divalproex and barbiturates should be switched to other drugs before pregnancy when possible. When seizures are controlled, maintenance medication may be reduced, if pos- sible, to the lowest dose that provides control. If seizures are not controlled, medications and dosages will need to be adjusted prior to pregnancy, if pos- sible. The frequency and severity of seizures may change during pregnancy. Regular monitoring by both an obstetrician and a neurologist is important. All women with epilepsy should be encouraged to register with the AED (Antiepileptic Drug) Pregnancy Registry.

Figure 15.12 summarizes the mechanisms, adverse effects, and clinical pearls of the antiepileptic drugs.