TABLE 58.3 Predictors of Intractable Epilepsy

Very young at onset (<2 yr)
Frequent generalized seizures
Failure to achieve control readily
Evidence of brain damage
A specific cause of the seizures
Severe EEG abnormality
Low IQ
Atonic atypical absence seizures

EEG, electroencephalogram.

Mortality is increased in persons with epilepsy, but the risk is incurred mainly by symptomatic cases in which higher death rates are related primarily to the underlying disease rather than to epilepsy. Accidental deaths, especially drowning, are more common, however, in all patients with epilepsy. Sudden unexplained death is nearly 25 times more common in patients with epilepsy than in the general population; estimates of incidence rates range from 1 in 500 to 1 in 2,000 per year. Severe epilepsy, uncontrolled generalized convulsions, especially nocturnal, and need for multiple AEDs are risk factors.

INITIAL DIAGNOSTIC EVALUATION

The diagnostic evaluation has three objectives: to determine if the patient has epilepsy; to classify the type of epilepsy and identify an epilepsy syndrome, if possible; and to define the specific underlying cause. Accurate diagnosis leads directly to proper treatment and formulation of a rational plan of management. The differential diagnosis is considered in Section II, Chapter 5.

Because epilepsy comprises a group of conditions and is not a single homogeneous disorder and because seizures may be symptoms of both diverse brain disorders and an otherwise normal brain, it is neither possible nor desirable to develop inflexible guidelines for what constitutes a standard or minimal diagnostic evaluation. The clinical data from the history and physical examination should allow a reasonable determination of probable diagnosis, seizure and epilepsy classification, and likelihood of underlying brain disorder. Based on these considerations, diagnostic testing should be undertaken selectively.

HISTORY AND EXAMINATION

A complete history is the cornerstone for establishing a diagnosis of epilepsy. Because patients frequently have no or only limited recall of their attacks, it is important to obtain additional information from family members or friends who have witnessed seizures. An adequate history should provide a clear picture of the clinical features of the seizures and the sequence in which manifestations evolve; the course of the epileptic disorder; seizure precipitants, such as alcohol or sleep deprivation; risk factors for seizures, such as abnormal gestation, febrile seizures, family history of epilepsy, head injury, encephalitis or meningitis, and stroke; and response to previous treatment. In children, developmental history is important.

In describing the epileptic seizure, care should be taken to elicit a detailed description of any aura. The aura was once considered to be the warning of an impending attack, but it is actually a simple partial seizure made apparent by subjective feelings or experiential phenomena observable only by the patient. Auras precede many complex partial or generalized seizures and are experienced by 50% to 60% of adults with epilepsy. Auras confirm the suspicion that the seizure begins locally within the brain; they may also provide direct clues about the location or laterality of the focus. Information about later events in the seizure usually are obtained from an observer because of the patient's impaired awareness or frank loss of consciousness or because of postictal amnesia, even though responses to questions during the seizure indicate preserved responsiveness.

The nature of repetitive automatic or purposeless movements (automatisms), sustained postures, presence of myoclonus, and the duration of the seizure help to delineate specific seizure types or epileptic syndromes. Nonspecific postictal findings of lethargy and confusion must be distinguished from focal neurologic abnormalities, such as hemiparesis or aphasia, which could point to the hemisphere of seizure onset.

Information about risk factors (Fig. 58.4) may suggest a particular cause and assist in prognosis. In addition to these risk factors, migraines with auras and depression have been reported to be independent risk factors for unprovoked seizures. Discussion of risk factors with parents may be necessary because children or adults

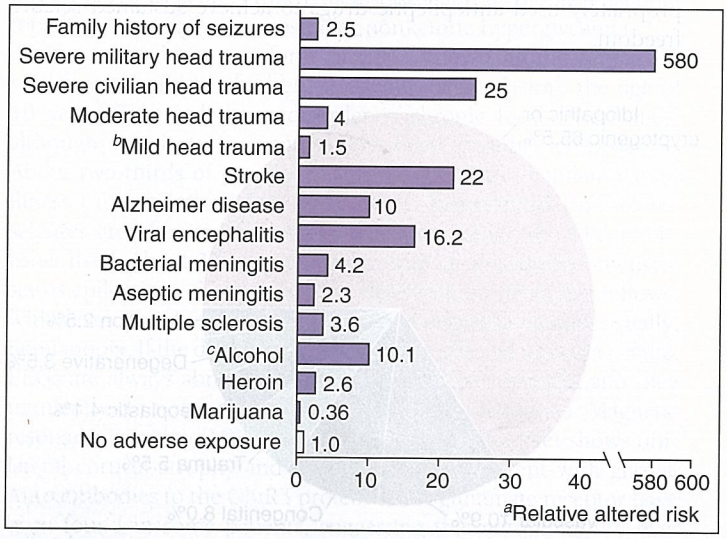

FIGURE 58.4 Risk factors for epilepsy. [a]Relative to people without these adverse exposures. [b]Not statistically significant. [c]One pint of 80 proof, 2.5 bottles of wine. (From Hauser WA, Hesdorffer DC. *Epilepsy: Frequency, Causes and Consequences*. New York: Demos; 1990.)

may be uninformed about, or may not recall, early childhood events, such as perinatal encephalopathy, febrile seizures, brain infections, head injuries, or intermittent absence seizures. Age at seizure onset and course of the seizure disorder should be clarified because these features differ in the various epilepsy syndromes.

Findings on neurologic examination are usually normal in patients with epilepsy but occasionally may provide etiologic clues. Focal signs indicate an underlying cerebral lesion. Asymmetry of the hand or face may indicate localized or hemispheric cerebral atrophy contralateral to the smaller side. Phakomatoses are commonly associated with seizures and are suggested by café au lait spots, facial angioma, conjunctival telangiectasia, hypopigmented macules, fibroangiomatous nevi, or lumbosacral shagreen patches.

ELECTROENCEPHALOGRAPHY

Because epilepsy is fundamentally a physiologic disturbance of brain function, the EEG is the most important laboratory test in evaluating patients with seizures. The EEG helps both to establish the diagnosis of epilepsy and to characterize specific epileptic syndromes. EEG findings may also help in management and in prognosis.

Epileptiform discharges (spikes and sharp waves) are highly correlated with seizure susceptibility and can be recorded on the first EEG in about 50% of patients. Similar findings are recorded in only 1% to 2% of normal adults and in a somewhat higher percentage of normal children. When multiple EEGs are obtained, epileptiform abnormalities eventually appear in 60% to 90% of adults with epilepsy, but the yield of positive studies does not increase substantially after three or four tests. Prolonged ambulatory or inpatient recordings increase the yield of interictal epileptiform abnormalities both because of the longer sampling times but also because complete sleep–wake cycles are included. It is important to remember, therefore, that 10% to 40% of patients with epilepsy do not show epileptiform abnormalities on routine EEG. Thus, a normal or nonspecifically abnormal EEG never excludes the diagnosis. Sleep, hyperventilation, photic stimulation, and special electrode placements are routinely used to increase the probability of recording epileptiform abnormalities. Different and distinctive patterns of epileptiform discharge occur in specific epilepsy syndromes as summarized in Chapter 25.

BRAIN IMAGING

MRI should be performed in all patients older than age 18 years and in children with abnormal development, abnormal findings on physical examination, or seizure types that are likely to be manifestations of symptomatic epilepsy. CT will often miss common epileptogenic lesions such as hippocampal sclerosis, cortical dysplasia, and cavernous malformations. Because CT is very sensitive for detecting brain calcifications, a noncontrast CT (in addition to MRI) may be helpful in patients at risk for neurocysticercosis.

Routine imaging is not necessary for children with idiopathic epilepsy, including the benign focal epilepsy syndromes (see section "Benign Epilepsy Syndromes"). Brain MRI, although more costly, is more sensitive than CT in detecting potentially epileptogenic lesions, such as cortical dysplasia, hamartomas, differentiated glial tumors, and cavernous malformations. Both axial and coronal planes should be imaged using both T1 and T2 sequences. Gadolinium injection does not increase the sensitivity for detecting cerebral lesions but may assist in differentiating possible causes.

Imaging in the coronal plane perpendicular to the long axis of the hippocampus and other variations in technique have improved the detection of hippocampal atrophy and gliosis, findings that are highly correlated with mesial temporal sclerosis (Fig. 58.5) and an epileptogenic temporal lobe. An even more sensitive measure of hippocampal atrophy is MRI measurement of the volume of the hippocampus. Hippocampal volume measurements in an individual patient then can be compared with those of normal control subjects. In patients being considered for surgery, interictal

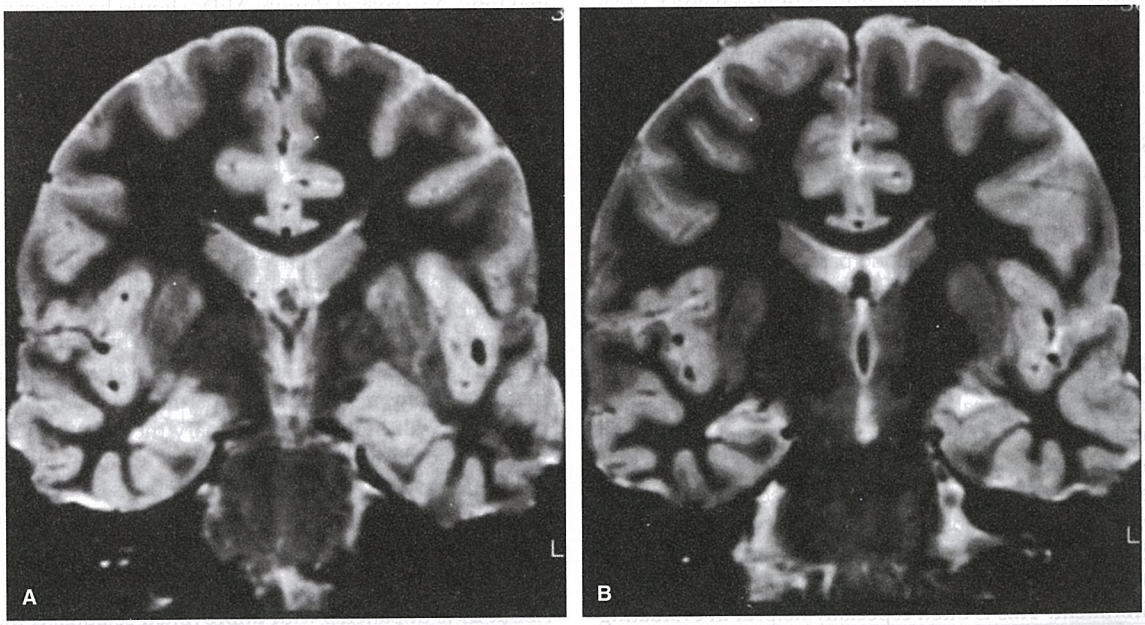

FIGURE 58.5 Mesial temporal sclerosis. **A,B:** Short-tau inversion recovery (STIR) coronal magnetic resonance images through the temporal lobes show increased signal and decreased size of right hippocampus as compared with left. These findings are characteristic of mesial temporal sclerosis. Note incidental focal dilatation of left choroid fissure, which represents a choroid fissure cyst and is a normal variant. (Courtesy of Dr. S. Chan, Columbia University College of Physicians and Surgeons, New York, NY.)

positron emission tomography (PET) scans can add valuable localizing information, especially when the MRI scan is negative. Single-photon emission computed tomography (SPECT) scans are also used, although resolution is less than either MRI or PET. Subtraction ictal SPECT co-registered with MRI (SISCOM) is also helpful in localizing the epileptogenic brain region in some cases.

OTHER LABORATORY TESTS

Routine blood tests are necessary in newborns and in older patients with acute or chronic systemic disease to detect abnormal electrolyte, glucose, calcium, or magnesium values or impaired liver or kidney function that may contribute to seizure occurrence. They are rarely diagnostically useful in healthy children or adults. Serum electrolytes, liver function tests, and a complete blood count (CBC) should be obtained when infectious or metabolic abnormalities are suspected, but they are useful mainly as baseline studies before initiating AED treatment.

Any suspicion of meningitis or encephalitis mandates lumbar puncture. Urine or blood toxicologic screens should be considered when otherwise unexplained new-onset generalized seizures occur.

LONG-TERM MONITORING

The most direct and convincing evidence of an epileptic basis for a patient's episodic symptoms is the electrographic recording of a seizure discharge during a typical behavioral attack. Such recordings are especially necessary if the history is ambiguous, EEGs are repeatedly normal or nonspecifically abnormal, and reasonable treatment has failed. Because most patients have seizures infrequently, routine EEG rarely records an attack. Long-term monitoring permits continuous EEG recording for extended periods, thus increasing the likelihood of recording seizures or interictal epileptiform discharges. Two methods of long-term monitoring are now widely available: simultaneous closed-circuit television (CCTV) and EEG (CCTV/EEG) monitoring and ambulatory EEG. Both have greatly improved diagnostic accuracy and the reliability of seizure classification, and both provide continuous recordings through one or more complete sleep–wake cycles, which increases the likelihood of capturing actual ictal events. Each has its own specific advantages and disadvantages. The method chosen depends on the question posed by a particular patient.

Long-term monitoring using CCTV/EEG, usually in a specially designed hospital unit, is the procedure of choice to document psychogenic seizures and other nonepileptic paroxysmal events. It can also establish electrical–clinical correlations, confirm seizure type, and direct further treatment including the localization of epileptogenic foci for possible resective surgery. The emphasis in monitoring units is usually on behavioral events, not interictal EEG activity. The availability of full-time technical or nursing staff ensures high-quality recordings and permits examination of patients during clinical events. AEDs can be discontinued safely to facilitate seizure occurrence. Computerized detection programs are used to screen EEG continuously for epileptiform abnormalities and subclinical seizures.

Ambulatory EEG is another method for long-term monitoring that is designed for outpatient use in the patient's home, school, or work environment. This is often especially helpful in evaluating children who are usually more comfortable in their familiar and unrestricted home environments. The major limitations of ambulatory monitoring are the variable technical quality resulting from lack of expert supervision and maintenance of electrode integrity, frequent distortion of EEG data by environmental contaminants, and the absence of video documentation of behavioral changes. Ambulatory monitoring is most useful in documenting interictal epileptiform activity when routine EEGs have been repeatedly negative or in recording ictal discharges during typical behavioral events. It may also reveal the presence of unrecognized electrographic seizures (particularly absences) if frequent. At the present time, however, ambulatory EEG is not a substitute for CCTV/EEG monitoring, especially when psychogenic seizures are an issue or when patients are being evaluated for epilepsy surgery.

MEDICAL TREATMENT

Therapy of epilepsy has three goals: (1) to eliminate seizures or reduce their frequency to the maximum extent possible, (2) to avoid side effects associated with long-term treatment, and (3) to assist the patient in maintaining or restoring normal psychosocial and vocational adjustment. No medical treatment now available can induce a permanent remission ("cure") or prevent development of epilepsy by altering the process of epileptogenesis.

The decision to institute AED therapy should be based on a thoughtful and informed analysis of the issues involved. Isolated infrequent seizures, whether convulsive or not, probably pose little medical risk to otherwise healthy persons. However, even relatively minor seizures, especially those associated with loss or alteration of alertness, can be associated with many psychosocial, vocational, and safety ramifications. Finally, the probability of seizure recurrence varies substantially among patients, depending on the type of epilepsy and any associated neurologic or medical problems. Drug treatment, on the other hand, carries a risk of adverse effects, which approaches 30% after initial treatment. Treatment of children raises additional issues, especially the unknown effects of long-term AED use on brain development, learning, and behavior.

These considerations mean that although drug treatment is indicated and is beneficial for most patients with epilepsy, certain circumstances call for AEDs to be deferred or used only for a limited time. As a rule of thumb, AEDs should be prescribed when the potential benefits of treatment clearly outweigh possible adverse effects of therapy.

ACUTE SYMPTOMATIC SEIZURES

These seizures are caused by, or associated with, an acute medical or neurologic illness (see Chapter 6). A childhood febrile seizure is the most common example of an acute symptomatic seizure, but other frequently encountered causes include metabolic or toxic encephalopathies, head trauma, and acute brain infections. Prophylactic phenytoin has been shown to reduce the frequency of seizures in patients with severe traumatic brain injury from 14% to 4% during the first week after injury [**Level 1**].[2] To the extent that these conditions resolve without permanent brain damage, seizures are usually self-limited. The primary therapeutic concern in such patients should be identification and treatment of the underlying disorder. If AEDs are needed to suppress seizures acutely, they generally do not need to be continued after the patient recovers.

THE SINGLE SEIZURE

About 25% of patients with unprovoked seizures come to a physician after a single attack, nearly always a generalized tonic–clonic seizure. Most of these people have no risk factors for epilepsy, have normal findings on neurologic examination, and have a normal first EEG. Only about 25% of such patients later develop epilepsy. For this group, the need for treatment is questionable. For many years,

no convincing data indicated any beneficial effect of treatment on preventing recurrence. In 1993, a large multicenter randomized study from Italy convincingly demonstrated that AEDs reduce the risk of relapse after the first unprovoked convulsive seizure. Among nearly 400 children and adults, treatment within 7 days of a first seizure was followed by a recurrence rate of 25% at 2 years. In contrast, untreated patients had a recurrence rate of 51%. When patients with previous "uncertain spells" were excluded from the analysis, treatment benefit was still evident, but the magnitude of the effect was reduced to a recurrence rate of 30% in the treated group and 42% in untreated patients.

Although treatment of first seizures reduces the relapse rate even in low-risk patients, there is no evidence that such treatment alters long-term prognosis. In 2015, a new evidence-based guideline for management of adults with a first unprovoked seizure identified the following risk factors for progression to epilepsy: a prior brain insult, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, and a nocturnal seizure [**Level 1**].[2] Clinicians' recommendations whether to initiate immediate AED treatment after a first seizure should be based on individualized assessments that weigh the risk of recurrence against the potential side effects of AED therapy and consider patient preferences. Immediate treatment will not improve the long-term prognosis for seizure remission but will reduce seizure risk over the subsequent 2 years. In most patients with idiopathic epilepsy, deferring treatment until a second seizure occurs is a reasonable and often preferable decision.

BENIGN EPILEPSY SYNDROMES

Several electroclinical syndromes begin in childhood and are associated with normal development, normal findings on neurologic examination, and normal brain imaging studies. They have a uniformly good prognosis for complete remission in mid to late adolescence without long-term behavioral or cognitive problems. The most common and best characterized of these syndromes is benign partial epilepsy of childhood with central–midtemporal sharp waves (rolandic epilepsy). Most seizures occur at night as secondarily generalized convulsions. Focal seizures occur during the day and are characterized by twitching of one side of the face, anarthria, salivation, and paresthesias of the face and inner mouth followed variably by hemiclonic movements or hemitonic posturing. Other generally benign syndromes include childhood epilepsy with occipital paroxysms and benign epilepsy with affective symptoms.

Because of the good prognosis, the sole goal of treatment in such cases is to prevent recurrence. Because many children, especially those who are older, tend to have only a few seizures, treatment is not always necessary. AEDs are usually reserved for children whose seizures are frequent or relatively severe or whose parents, or the children themselves, are frightened at the prospect of future attacks. With these considerations in mind, only about half the children with benign partial epilepsy require treatment.

ANTIEPILEPTIC DRUGS

Selection of Antiepileptic Drugs

Two nationwide collaborative Veterans Administration Cooperative Studies (1985 and 1992) compared the effectiveness of the then available major AEDs. In the 1985 study, carbamazepine, phenytoin, primidone, and phenobarbital were equally effective in controlling complex partial and secondarily generalized seizures [**Level 1**].[3] In the 1992 study, carbamazepine was slightly more effective than valproate in treating complex partial seizures, but both drugs were of equal efficacy in controlling secondarily generalized seizures [**Level 3**].[4] These studies also demonstrated that despite their relatively uniform ability to suppress seizures, the drugs had different risks of adverse effects. More recently, there have been randomized trials in patients with partial seizures comparing the effectiveness of gabapentin, lamotrigine, topiramate, or oxcarbazepine to that of carbamazepine and phenytoin. None has shown definite superiority, although many have demonstrated that the newer agents have improved tolerability. *A survey of epilepsy experts in North America found that carbamazepine remains the drug of first choice for partial seizures when both efficacy and tolerability are considered.* Gabapentin, pregabalin, lamotrigine, topiramate, oxcarbazepine, levetiracetam, and phenytoin remain reasonable alternatives for many patients. The SANAD trial, a large open-label study, randomized patients with focal epilepsy to carbamazepine, lamotrigine, oxcarbazepine, or topiramate. Lamotrigine had a slight advantage in time to treatment failure, but as in previous comparative studies, the differences among agents in terms of effectiveness were minimal [**Level 1**].[5] Many smaller trials have directly compared various drugs against each other with similar findings; although there may be differences in tolerability, there are no clear advantages in efficacy when an appropriate agent is used at a therapeutic dose [**Level 1**].[6]

In general, valproate is the drug of choice for generalized-onset seizures and can be used advantageously as monotherapy when several generalized seizure types coexist (Table 58.4). Lamotrigine, levetiracetam, topiramate, and zonisamide are suitable alternatives if valproate is ineffective or not tolerated. A second arm of the SANAD trial compared the effectiveness of valproate, lamotrigine, and topiramate in patients with all types of generalized or unclassified seizures. Valproate was found to be slightly more effective overall, especially for idiopathic epilepsy, although the differences were minimal [**Level 1**].[7] Phenytoin, carbamazepine, and oxcarbazepine are useful in suppressing generalized tonic–clonic seizures, but the response is less predictable than that with valproate. Carbamazepine, phenytoin, gabapentin, and lamotrigine can aggravate myoclonic seizures; all of these except lamotrigine also sometimes exacerbate absence seizures. Tiagabine can aggravate or induce absence

TABLE 58.4 Drugs Used in Treating Different Types of Seizures

Type of Seizure	Drugs[a]
Localization related epilepsy	
Simple and complex partial; secondarily generalized	Carbamazepine, lamotrigine, topiramate, levetiracetam, lacosamide, oxcarbazepine, pregabalin, valproate, gabapentin, zonisamide, phenytoin, primidone, phenobarbital, perampanel, ezogabine, clobazam
Primary generalized seizures	
Tonic–clonic	Valproate, lamotrigine, topiramate, levetiracetam, zonisamide, carbamazepine, oxcarbazepine, phenytoin
Absence	Valproate, lamotrigine, ethosuximide, zonisamide
Myoclonic	Valproate, clonazepam, levetiracetam
Tonic	Valproate, felbamate, clonazepam, zonisamide, rufinamide

[a]Not all drugs have FDA approval for listed uses.

seizures. Ethosuximide is as effective as valproate in controlling absence seizures and has fewer side effects. Ethosuximide is ineffective against tonic–clonic seizures, however, so its main use is as an alternative to valproate in patients who have only absence seizures.

Many of the newer AEDs have been shown to be effective as adjunctive or add-on therapy for patients with seizures that are refractory to a single medication. Gabapentin can be effective for the treatment of mixed seizure disorders, and gabapentin, lamotrigine, oxcarbazepine, and topiramate for the treatment of refractory partial seizures in children. Evidence also suggests that lamotrigine and topiramate are also effective for adjunctive treatment of idiopathic generalized epilepsy in adults and children, as well as treatment of the Lennox Gastaut syndrome [**Level 1**].[8]

Clobazam was recently U.S. Food and Drug Administration (FDA) approved for add-on therapy in severe epilepsies such as Lennox–Gastaut syndrome. It is also effective in focal epilepsies that are refractory to other medications and has been widely prescribed worldwide for this indication. Vigabatrin was approved by the FDA for treating infantile spasms in children 1 month to 2 years of age.

Of the more recently introduced antiepileptic medications, lacosamide, ezogabine, and perampanel have been approved for use in focal epilepsies refractory to other medications, and rufinamide was additionally approved to treat seizures associated with Lennox–Gastaut syndrome.

Elderly patients with epilepsy require special consideration because of age-related changes in both pharmacokinetic profiles and pharmacodynamic characteristics. Relevant physiologic changes include decreased hepatic metabolism and plasma protein binding, decreased renal clearance, and slower gastrointestinal motility and absorption. There is greater sensitivity to both desirable and undesirable effects on brain function. Additionally, concurrent medical illnesses are common, and as a result, most elderly patients take multiple drugs, which increase the likelihood of clinically significant drug interactions. Several clinical trials involving elderly patients, including a large Veterans Administration cooperative study, have found that lamotrigine and gabapentin are better tolerated than carbamazepine, although, as in younger patients, differences in effectiveness, if any, are small.

Adverse Effects of Antiepileptic Drugs

All AEDs have undesirable effects in some patients. Although interindividual variation occurs, most adverse drug effects are mild and dose related. Many are common to virtually all AEDs, especially when treatment is started. These include sedation, mental dulling, impaired memory and concentration, mood changes, gastrointestinal upset, and dizziness. The incidence of particular adverse effects varies with the individual agent. In general, sedation and cognitive effects are less likely with lamotrigine or gabapentin than with older agents, especially in elderly persons. Some adverse effects are relatively specific for particular drugs.

DOSE-RELATED SIDE EFFECTS

These typically appear when a drug is first given or when the dosage is increased. They usually, but not always, correlate with blood concentrations of the parent drug or major metabolites (Table 58.5). Dose-related side effects are always reversible on lowering the dosage or discontinuing the drug. An exception to this is the peripheral vision loss with vigabatrin, which may progress despite stopping the drug. Adverse effects frequently determine the limits of treatment with a particular drug and have a major influence on compliance with the prescribed regimen. Because dose-related side effects are broadly predictable, they are often the major differentiating feature in choosing among otherwise equally effective therapies.

IDIOSYNCRATIC SIDE EFFECTS

Idiosyncratic responses account for most serious and virtually all life-threatening adverse reactions to AEDs. Many AEDs can cause similar serious side effects (see Table 58.5), but with the exception of rash, these are fortunately rare. For example, the risk of carbamazepine-induced agranulocytosis or aplastic anemia is about 2 per 575,000; with felbamate, the risk of aplastic anemia may be as high as 1 per 5,000. Idiosyncratic reactions are not dose related; rather they arise either from an immune-mediated reaction to the drug or from poorly defined individual factors, largely genetic, that convey an unusual sensitivity to the drug. An example of the genetic mechanism is valproate-induced fatal hepatotoxicity. Valproate, like most AEDs, is metabolized in the liver, but several biochemical pathways are available to the drug. Clinical and experimental data indicate that one of these pathways results in a hepatotoxic compound that may accumulate and lead to microvesicular steatosis with necrosis. The extent to which this pathway is involved in biotransformation is age dependent and promoted by concurrent use of other drugs that are eliminated in the liver. Thus, most patients who have had fatal hepatotoxicity were younger than 2 years of age and treated with polytherapy (Table 58.6). In addition, most had severe epilepsy associated with mental retardation, developmental delay, or congenital brain anomalies. No hepatic deaths have occurred in persons older than 10 years treated with valproate alone.

No laboratory test, certainly not untargeted routine blood monitoring, identifies individuals specifically at risk for valproate hepatotoxicity or any other drug-related idiosyncratic reaction. Clinical data, however, permit identification of groups of patients at increased risk for serious adverse drug reactions, including patients with known or suspected metabolic or biochemical disorders, a history of previous drug reactions, and medical illnesses affecting hematopoiesis or liver and kidney function.

Rash can occur with virtually any drug, and rarely, this results in Stevens–Johnson syndrome. The frequency of severe rash is about the same with carbamazepine, phenytoin, phenobarbital, and (if started slowly over several weeks) lamotrigine. There is some cross-reactivity among these drugs, so that a patient who develops a rash with one has a slightly increased risk of developing a rash with another. Rash is unusual with valproate, gabapentin, pregabalin, or levetiracetam. To date, life-threatening idiosyncratic effects have not been reported with gabapentin, pregabalin, topiramate, oxcarbazepine, tiagabine, or levetiracetam.

Antiepileptic Drug Pharmacology

Table 58.7 provides summary information about dose requirements, pharmacokinetic properties, and therapeutic concentration ranges for the major AEDs available in the United States. Of patients with epilepsy, 60% to 70% achieve satisfactory control of seizures with currently available AEDs, but fewer than 50% of adults achieve complete control without drug side effects. Many patients continue to have frequent seizures despite optimal medical therapy.

Treatment should start with a single AED chosen according to the type of seizure or epilepsy syndrome and then be adjusted as necessary, by considerations of side effects, required dosing schedule, and cost. Phenytoin, phenobarbital, gabapentin, and levetiracetam can be loaded acutely. There is evidence either from comparative or dose-controlled trials that gabapentin, lamotrigine, topiramate,

TABLE 58.5 Toxicity of Antiepileptic Drugs

Dose-Related Adverse Effects
Systemic Toxicity
Gastrointestinal (dyspepsia, nausea, diarrhea; esp. valproate, zonisamide)
Benign elevation in liver enzymes (esp. valproate, phenobarbital, phenytoin, carbamazepine, oxcarbazepine)
Benign leukopenia (esp. carbamazepine)
Gingival hypertrophy (esp. phenytoin)
Weight gain (esp. valproate, gabapentin, pregabalin)
Anorexia and weight loss (esp. felbamate, topiramate, zonisamide)
Hair loss, change in hair texture (esp. valproate)
Hirsutism (esp. phenytoin, valproate)
Hyponatremia (esp. carbamazepine, oxcarbazepine)
Coarsening of facial features (esp. phenytoin)
Dupuytren contracture, frozen shoulder
Osteoporosis (esp. phenytoin, carbamazepine, valproate)
Impotence (esp. phenobarbital, carbamazepine)
Neurologic Toxicity
Drowsiness, sedation
Impaired cognition (memory, concentration; esp. topiramate)
Depression and mood changes (esp. phenobarbital, levetiracetam, topiramate)
Irritability, hyperactivity
Insomnia (esp. felbamate)

Dose-Related Adverse Effects
Neurologic Toxicity *(continued)*
Peripheral visual field restriction (vigabatrin)
Dizziness/vertigo
Nystagmus, diplopia
Ataxia
Tremor, asterixis
Dyskinesias, dystonia, myoclonus
Dysarthria
Headache
Sensory neuropathy
Systemic Toxicity
Rash (rare with valproate, gabapentin, levetiracetam, pregabalin)
Exfoliative dermatitis
Erythema multiforme
Stevens–Johnson syndrome (esp. lamotrigine)
Agranulocytosis
Aplastic anemia (esp. felbamate)
Hepatic failure (esp. felbamate, valproate)
Pancreatitis
Connective tissue disorders
Thrombocytopenia (esp. valproate)
Pseudolymphoma syndrome

and oxcarbazepine have efficacy as monotherapy in newly diagnosed adolescents and adults with either partial or mixed seizure disorders. There is also evidence that lamotrigine is effective for newly diagnosed absence seizures in children. In the absence of status epilepticus (Chapter 6), AEDs should be started at low dosages to minimize acute toxicity. They can then be increased according to the patient's tolerance and the drug's pharmacokinetics. The initial target dose should produce a serum concentration in the low to mid therapeutic range. Further increases can then be titrated according to the patient's clinical progress, which is measured mainly by seizure frequency and the occurrence of drug side effects. A drug should not be judged a failure unless seizures remain uncontrolled at the maximal tolerated dosage, regardless of the blood level.

TABLE 58.6 Effect of Age and Treatment on Risk of Developing Fatal Valproate Hepatotoxicity

Age	Monotherapy	Polytherapy
<2 yr	1/7,000	1/500
>2 yr	1/80,000	1/25,000

Modified from Dreifuss FE, Santilli N, Langer DH, et al. *Neurology.* 1987;37:379–385.

Dosage changes generally should not be made until the effects of the drug have been observed at steady-state concentrations (a time about equal to five drug half-lives). If the first drug is ineffective, an appropriate alternative should be gradually substituted (see Table 58.4). Combination treatment using two drugs should be attempted only when monotherapy with primary AEDs fails. Combination therapy is sometimes effective, but the price of improved seizure control is often additional drug toxicity. Sometimes, combination therapy with relatively nonsedating drugs (e.g., carbamazepine, lamotrigine, gabapentin, or valproate) is preferable to high-dose monotherapy with a sedating drug (e.g., phenobarbital or primidone). When used together, carbamazepine and lamotrigine result in a pharmacodynamic interaction that often produces neurotoxicity at dosages that are usually well tolerated when either drug is used alone.

Dosing intervals should usually be less than one-third to one-half the drug's half-life to minimize fluctuations between peak and trough blood concentrations. Large fluctuations can result in drug-induced side effects at peak levels and in breakthrough seizures at trough concentrations. Sometimes, however, a drug has a relatively long pharmacodynamic half-life, so that twice a day dosing is reasonable even if the pharmacokinetic half-life is short. This is typically the case with valproate, tiagabine, pregabalin, gabapentin, and levetiracetam. Extended-release formulations of most commonly used AEDs are available, which allow less frequent dosing and decreased peak and trough levels, thereby potentially

TABLE 58.7 Antiepileptic Drugs: Dosage and Pharmacokinetic Data

Drug	Usual Adult Dose 24 h (mg)	Half-life (h)	Usually Effective Plasma Concentration (μg/mL)	Time-to-Peak Concentration (h)	Bound Fraction (%)
Phenytoin	300–400	22	10–20	3–8	90–95
Carbamazepine	800–1,600	8–22	8–12	4–8	75
Phenobarbital	90–180	100	15–40	2–8	45
Valproate	1,000–3,000	15–20	50–120	3–8	80–90
Ethosuximide	750–1,500	60	40–100	3–7	<5
Felbamate	2,400–3,600	14–23	20–140	2–6	25
Gabapentin	1,800–3,600	5–7	4–16[a]	2–3	<5
Lamotrigine	100–500	12–60[b]	2–16[a]	2–5	55
Topiramate	200–400	19–25[b]	4–10[a]	2–4	9–17
Vigabatrin	1,000–3,000	5–7	NE	1–4	5
Tiagabine	32–56	5–13	NE	1	95
Levetiracetam	1,000–3,000	6–8	5–45[a]	1	<10
Oxcarbazepine	900–2,400	8–10[c]	10–35[a]	3–13	40[c]
Zonisamide	100–600	24–60[b]	10–40[a]	2–6	40
Pregabalin	150–600	5–7	NE	1	<5
Lacosamide	200–400	12–16	NE	1–4	<15
Rufinamide	2,400–3,200	6–10	NE	4–6	34
Clobazam	10–40	36–42	NE	0.5–4	80–90
Ezogabine	600–1,200	7–11	NE	0.5–2	80
Perampanel	8–12	105	NE	0.5–2.5	95

[a]Not established; corresponds to usual range in patients treated with recommended dose.
[b]Highly dependent on concurrently administered drugs.
[c]Of metahydroxy derivative, the active metabolite.
NE, not established.

improving tolerability and compliance. Bioavailability is not necessarily equivalent to immediate-release formulations, and different extended-release delivery systems with alternate manufacturers of the same drug can also create variation in peak and trough levels, as well as total absorption.

Therapeutic drug monitoring has greatly improved the care of patients with epilepsy, but published therapeutic ranges are only guidelines. Most patients whose drug concentrations are within a standard therapeutic range usually achieve adequate seizure control with minimal side effects, but notable exceptions occur. Some patients develop unacceptable side effects at "subtherapeutic" concentrations; others benefit from "toxic" concentrations without adverse effects.

Determining serum drug concentrations when seizure control has been achieved or when side effects appear can assist future management decisions. Drug levels are also useful in documenting compliance and in assessing the magnitude and significance of known or suspected drug interactions. Therapeutic drug monitoring is an essential guide to treating neonates, infants, young children, elderly persons, and patients with diseases (e.g., liver or kidney failure) or physiologic conditions (e.g., pregnancy) that alter drug pharmacokinetics. Although the total blood concentrations that are routinely reported are satisfactory for most indications, unbound (free) concentrations are useful when protein binding is altered, as in renal failure, pregnancy, extensive third-degree burns, and combination therapy using two or more drugs that are highly bound to serum proteins (e.g., phenytoin, valproate, tiagabine).

Specific Drugs

Phenytoin is unique among AEDs because it exhibits nonlinear elimination at therapeutically useful serum concentrations. That is, hepatic enzyme systems metabolizing phenytoin become increasingly saturated at plasma concentrations greater than 10 to 12 μg/mL, and metabolic rate approaches a constant value at high concentrations. With increasing doses, phenytoin plasma concentrations rise exponentially (Fig. 58.6), so that steady-state concentration at one dose cannot be used to predict directly the steady-state concentration at a higher dose. Clinically, this requires cautious titration within the therapeutic range, using dose increments of 30 mg to avoid toxic effects.

Carbamazepine induces activation of the enzymes that metabolize it. The process, termed *autoinduction*, is time dependent. When carbamazepine is first introduced, the half-life approximates 30 hours. With increasing hepatic clearance in the first 3 to 4 weeks of therapy, however, the half-life shortens to 11 to 20 hours. As a result, the starting dose should be low and then increased gradually, and dosing should be frequent (three or four times daily). Extended-release formulations permit twice a day administration. The principal metabolite is carbamazepine-10,11-epoxide, which is pharmacologically active. Under certain circumstances (e.g., when

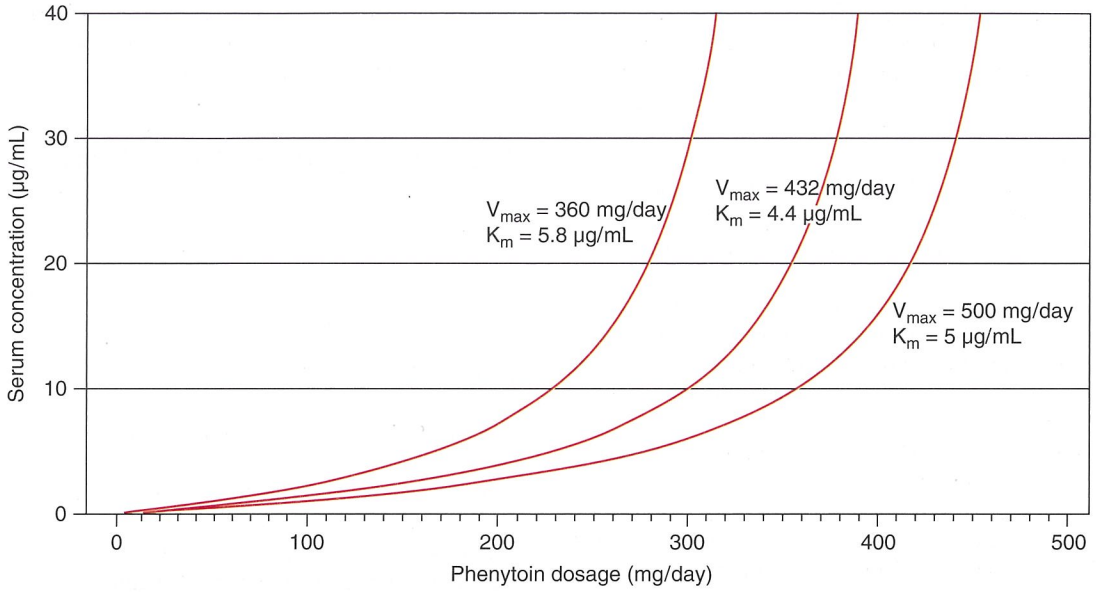

FIGURE 58.6 Phenytoin dose concentration curves from three representative adult patients. Note the markedly nonlinear relationship in the 200- to 400-mg dose range. Careful dose titration is necessary in this portion of the curve to avoid neurotoxicity. K_m, Michaelis–Menten constant; V_{max}, maximum elimination rate.

coadministered with valproate or felbamate), the epoxide metabolite accumulates selectively, thereby producing neurotoxic effects even though the plasma concentration of the parent drug is in the therapeutic range or even low.

Valproate is highly bound to plasma proteins, but the binding is concentration dependent and nonlinear. The unbound fraction increases at plasma concentrations greater than 75 µg/mL because protein-binding sites become saturated. For example, doubling the plasma concentration from 75 to 150 µg/mL can result in a more than sixfold rise in concentration of free drug (from 6.5 to 45 µg/mL). Therefore, as the dose of valproate is increased, side effects may worsen rapidly because of the increasing proportion of unbound drug. Furthermore, adverse effects may vary in the course of a single day or from day to day because concentrations of unbound drug fluctuate despite seemingly small changes in total blood levels. Additionally, circulating fatty acids displace valproate from protein-binding sites. If fatty acid levels are high, the amount of unbound valproate increases. Lamotrigine and felbamate prolong the half-life of valproate and therefore a reduced dosage is typically necessary when these drugs are added.

Gabapentin requires an intestinal amino acid transport system for absorption. Because the transporter is saturable, the percentage of drug that is absorbed after an oral dose decreases with increasing dosage. More frequent dosing schedules using smaller amounts may therefore be necessary to increase blood levels. When dosages above 3,600 mg/day are used, blood levels can be helpful in demonstrating that an increase in dosage is reflected in an increased serum concentration. Gabapentin does not interact to any clinically significant degree with any other drugs, which makes it especially useful when AED polytherapy is necessary and in patients with medical illnesses that also require drug treatment. It is not metabolized in the liver, but as it is excreted unchanged by the kidneys, dose adjustment is required in patients with renal failure. *Pregabalin* is structurally and mechanistically similar to gabapentin but does not show dose-dependent absorption. It has increased potency compared with gabapentin and can be effective with twice-daily dosing.

Lamotrigine is highly sensitive to coadministration of many other AEDs. Enzyme-inducing agents, such as phenytoin and carbamazepine, decrease the half-life of lamotrigine from 24 to 16 hours (or less) as do oral contraceptive agents. In contrast, enzyme inhibition by valproate increases the half-life of lamotrigine to 60 hours. Therefore, lamotrigine dosing depends very much on whether it is used as monotherapy or in combination with other AEDs. Lamotrigine concentrations are also lowered by administration of oral contraceptives, and levels can decrease dramatically during the latter months of pregnancy requiring frequent monitoring and dose adjustment. Lamotrigine has little or no effect on other classes of drugs. Rash occurs in about 10% of patients; it is more common in children and rarely leads to Stevens–Johnson syndrome. The incidence of rash can be minimized by slow titration schedules.

Levetiracetam, like gabapentin, has no appreciable interactions with other drugs and therefore has advantages in medically complicated patients. The plasma half-life is 6 to 8 hours, but clinical trials support twice-daily dosing, possibly owing to a longer pharmacodynamic half-life. Metabolism occurs in the liver, and there is also renal clearance. Adverse effects are generally mild and self-limited, although mood changes and even psychosis occur in a small subset of patients. No life-threatening idiosyncratic reactions have yet been described.

Oxcarbazepine is structurally similar to carbamazepine, but it is metabolized by a different pathway. As a result, there is no epoxide metabolite that is responsible for some of the adverse effects of carbamazepine. Although individual patients may tolerate oxcarbazepine better than carbamazepine, the overall profiles of the two drugs are similar, including development of leukopenia (usually transient, asymptomatic, and benign), mild increase in hepatic enzymes, and hyponatremia. Pharmacologic half-life of the active metabolite, a metahydroxy derivative (MHD), is 8 to 10 hours. Clinical studies support twice-daily dosing, although peak toxicity can occur when this is done at higher dosages.

Topiramate is affected by other AEDs taken concurrently. Carbamazepine, phenytoin, and phenobarbital shorten its half-life;

valproate has little effect. Topiramate does not affect most other drugs, although phenytoin blood levels may increase by 25%. Adverse cognitive effects, especially word-finding difficulty and impaired memory, frequently limit the dosage patients can tolerate. These are usually dose dependent and can be minimized with slow titration schedules. Cognitive effects are also less common in monotherapy. Glaucoma, anhydrosis, and renal stones occur rarely. Doses above 400 mg/day do not usually lead to better seizure control but are associated with an increasing incidence of side effects.

Tiagabine is highly bound to serum proteins and will therefore displace other drugs (e.g., phenytoin, valproate) that are also protein bound. Other drugs do not affect tiagabine's metabolism significantly. Gastrointestinal side effects usually limit the rate at which the dosage may be increased.

Zonisamide is affected by other drugs that induce hepatic enzymes. As monotherapy, zonisamide's half-life is about 60 hours. When coadministered with enzyme-inducing drugs, its half-life can be reduced to 24 hours. In either case, once-daily dosing is appropriate. Although its metabolism occurs primarily in the liver, zonisamide itself does not appear to affect other drugs. Rash, renal stones, and anhydrosis are rare side effects.

Felbamate has a much higher risk of serious adverse reactions, including aplastic anemia and hepatic failure, than other AEDs. The actual risk has been difficult to estimate but is probably between 1 per 5,000 and 1 per 20,000 exposures. For this reason, its use is currently restricted to patients who are refractory to other agents and in whom the risk of continued seizures outweighs the risk of side effects. Use of felbamate is also limited by other common but less serious adverse effects, including anorexia, weight loss, insomnia, and nausea, and by numerous complex drug interactions. Nonetheless, felbamate remains useful in cases of severe epilepsy such as Lennox–Gastaut syndrome.

Lacosamide enhances the slow inactivation of sodium channels without affecting fast inactivation. It may prolong the PR interval, which can result in cardiac conduction problems. A baseline electrocardiogram (ECG) is suggested prior to initiating this drug.

Rufinamide is a triazole derivative whose exact mechanism is unknown. *In vitro* prolongs the inactive state of the sodium channels, thereby limiting repetitive firing of Na^+-dependent action potentials mediating anticonvulsant effects. Its use is limited largely to refractory generalized epilepsies, especially in controlling tonic seizures.

Clobazam has been used in many countries around the world, but it was only recently FDA approved in the United States for adjunctive treatment of Lennox–Gastaut syndrome. It is widely used off-label as adjunctive treatment for partial seizures. In catamenial epilepsy, it can be prescribed in doses of 20 to 30 mg daily for 10 days during the perimenstrual period. Serious reactions including Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN) have been reported.

Ezogabine is FDA approved as an adjunctive medicine in patients with partial seizures. All patients starting on this medication should undergo a baseline and periodic eye exams every 6 months including dilated funduscopy and visual acuity testing. Blue discoloration of the skin, especially of the lips and nail bed, has been reported. QT prolongation has also been observed, warranting monitoring with ECG especially in patients with electrolyte and cardiac abnormalities. This medicine can cause urinary retention and therefore is better avoided in elderly male patients with prostate enlargement.

Perampanel, which is FDA approved as an adjunctive medication in partial seizures, has a unique mechanism of action in that it is the first noncompetitive antagonist of the AMPA glutamate receptor. It comes with a boxed warning of dose-related serious neuropsychiatric events including homicidal thoughts and aggression. Being both an inducer and a substrate of the CYP3A4 enzymes, drug interactions with other antiseizure medications exist.

Discontinuing Antiepileptic Drugs

Epidemiologic studies indicate that 60% to 70% of patients with epilepsy become free of seizures for at least 5 years within 10 years of diagnosis. Similarly, prospective clinical trials of treated patients whose seizures were in remission for 2 years or more showed that a nearly identical percentage of patients remained seizure free after drug withdrawal [**Level 1**].[9] Chance of recurrence continues to decline with seizure freedom for 2 to 5 years. These studies also identified predictors that permit patients to be classified as being at low or high risk for seizure relapse after drug therapy ends. The risk of relapse was high if patients required more than one AED to control seizures, if seizure control was difficult to establish, if the patient had a history of generalized tonic–clonic seizures, and if the EEG was significantly abnormal when drug withdrawal was considered. Continued freedom from seizures is favored by longer seizure-free intervals (>4 years) before drug withdrawal is attempted, few seizures before remission, monotherapy, normal EEG, and no difficulty establishing seizure control.

All benign epilepsy syndromes of childhood carry an excellent prognosis for permanent drug-free remission. In contrast, JME has a high rate of relapse when drugs are discontinued, even in patients who have been seizure free for years. The prognosis for most other epilepsy syndromes is largely unknown.

Discontinuing AED therapy in appropriate patients can be considered when they have been seizure free for at least 2 years. The most powerful argument for stopping AEDs is concern about long-term systemic and neurologic toxicity, which can be insidious and not apparent for many years after a drug has been introduced. On the other hand, however, is the concern of the patient or family about seizure recurrence. Even a single seizure can have disastrous psychosocial and vocational consequences, particularly in adults. Therefore, the decision to withdraw drugs must be weighed carefully in the light of individual circumstances. If a decision is made to discontinue AEDs, we favor slow withdrawal, over 3 to 6 months, but this recommendation is controversial because few studies of different withdrawal rates have been conducted.

REPRODUCTIVE HEALTH ISSUES

Gender-based differences in AED pharmacokinetics, sex steroid hormones, and reproductive life events raise special issues for women with epilepsy. The management of pregnancy in a woman with epilepsy is discussed in detail in Chapter 124. This section focuses on the effects of reproductive hormones on seizures and on the effects of seizures and AEDs on reproductive health.

Although the prevalence of epilepsy is not higher in women, epilepsy in women can be specially affected by changes in reproductive steroids. Estrogen is a proconvulsant drug in animal models of epilepsy, whereas progesterone and its metabolites have anticonvulsant effects. Ovarian steroid hormones act at the neuronal membrane and on the genome to produce immediate and long-lasting effects on excitability. Estrogen reduces GABA-mediated inhibition, whereas progesterone enhances GABA effects. Estrogen also potentiates the action of excitatory neurotransmitters in some brain regions and increases the number of excitatory synapses. These dynamic and significant changes in neuronal excitability are

observed with changes in estrogen and progesterone concentrations similar to those observed in the human menstrual cycle.

Approximately one-third of women with epilepsy report patterns of seizure occurrence that relate to phases of the menstrual cycle (*catamenial seizures*). Women with catamenial seizures indicate that seizures are more frequent, or more severe, just before menstruation and during the time of menstrual flow. In some women, seizures also increase at ovulation. These are times in the menstrual cycle when estrogen levels are relatively high and progesterone concentration is relatively low. Several small clinical trials have described benefit from chronic progesterone therapy in women with catamenial seizure patterns. Changes in seizures related to puberty and menopause are not well understood.

The pharmacokinetics of some AEDs can complicate epilepsy management in women. AEDs that induce activity of the cytochrome P-450 enzyme system (carbamazepine, phenytoin, phenobarbital, primidone, and, to a lesser extent, topiramate and oxcarbazepine) interfere with the effectiveness of estrogen-based hormonal contraception. In women taking these drugs, the metabolism and binding of contraceptive steroids is enhanced, thus reducing the biologically active fraction of steroid hormone. The failure rate of oral contraceptive pills exceeds 6% per year in women taking enzyme-inducing AEDs, in contrast to a failure rate of less than 1% per year in medication-compliant women without epilepsy. A woman motivated to avoid pregnancy should consider using a contraceptive preparation containing 50 μg or more of an estrogenic compound or using an additional barrier method of contraception. Alternatively, she should discuss with her physician the possibility of selecting an AED that does not alter steroid metabolism or binding.

Reproductive health may be compromised in both women and men with epilepsy. Fertility rates for men and women with epilepsy are one-third to two-thirds those of men and women without epilepsy. Lower birth rates cannot be explained on the basis of lower marriage rates because marriage rates for women with epilepsy are now similar to those of nonepileptic women. Reduced fertility appears to be the direct result of a disturbance in reproductive physiology.

Men and women with epilepsy show a higher than expected frequency of reproductive endocrine disturbances. These include abnormalities both in the cyclic release and concentration of pituitary luteinizing hormone and prolactin and in the concentration of gonadal steroid hormones. Some of these abnormalities are likely to be a consequence of seizure activity. AEDs can also alter concentrations of gonadal steroids by affecting steroid hormone metabolism and binding. AEDs that increase steroid metabolism and binding reduce steroid hormone feedback at the hypothalamus and pituitary. AEDs that inhibit steroid metabolism (e.g., valproate) increase concentrations of steroid hormones, particularly androgens.

The polycystic ovary syndrome (PCOS) is a gynecologic disorder affecting approximately 7% of reproductive-age women. Women with epilepsy are at risk for developing features of this syndrome. Diagnostic requirements for PCOS are phenotypic or serologic evidence for hyperandrogenism and anovulatory cycles (Morrell, 2003). Phenotypic signs of hyperandrogenism include hirsutism, truncal obesity, and acne. Hirsutism presents as increased facial and body hair, coarsening of pubic hair with extension down the inner thigh, and male pattern scalp hair loss—temporal recession and thinning over the crown. Health consequences of PCOS include infertility, accelerated atherosclerosis, diabetes, and endometrial carcinoma, underscoring the importance of detection and treatment. As many as 30% of cycles in women with epilepsy are anovulatory, and anovulatory cycles appear to be most frequent in women receiving valproic acid (VPA). Women with epilepsy are more likely to have polycystic-appearing ovaries, which along with hyperandrogenism occur in as many as 40% of women with epilepsy receiving VPA. The long-term consequences of PCOS in women with epilepsy are unknown. Data such as these suggest that epilepsy and some AEDs individually affect fertility and that these effects may be additive. This implies that optimal therapy for epilepsy will consider disease–treatment effects on reproductive health.

Sexual dysfunction affects about one-third of men and women with epilepsy. Men report low sexual desire, difficulty achieving or maintaining an erection, or delayed ejaculation. Women with epilepsy can experience painful intercourse because of vaginismus and lack of lubrication. Although there are certainly psychosocial reasons for sexual dysfunction in some people with epilepsy, physiologic causes are demonstrable in others. Physiologic causes of sexual dysfunction include disruption of brain regions controlling sexual behavior by epileptogenic discharges, abnormalities of pituitary and gonadal hormones, and side effects of AEDs.

Although no anticonvulsant drug is free of teratogenic effects, the risk is low and generally less than that of uncontrolled seizures during pregnancy. The exceptions to this are valproate and topiramate, both of which are associated with increased risk of congenital malformations in prospective monotherapy studies. Valproate has also been shown to carry a dose-dependent risk of decreased IQ compared with phenytoin, carbamazepine, and lamotrigine. In all cases, the lowest effective dose should be used, and polypharmacy should be avoided [**Level 1**].[10] Women with epilepsy who have difficulty conceiving, irregular or abnormal menstrual cycles, midcycle menstrual bleeding, sexual dysfunction, obesity, or hirsutism should be referred for a reproductive endocrine evaluation. Men with sexual dysfunction or difficulty conceiving should also have an endocrine evaluation and semen analysis. All the reproductive disorders seen in people with epilepsy are potentially treatable.

BONE HEALTH

Persons with epilepsy are at greater risk for bone disease, which typically presents as pathologic fractures. Bone biochemical abnormalities described in people with epilepsy include hypocalcemia, hypophosphatemia, elevated serum alkaline phosphatase, elevated parathyroid hormone (PTH), and reduced levels of vitamin D and its active metabolites (Pack & Morrell, 2004). The most severe bone and biochemical abnormalities are found in patients receiving AED polytherapy and in those who have taken AEDs for a longer time. Effects are more pronounced with enzyme-inducing AEDs, especially phenytoin.

SURGICAL TREATMENT

Surgery should be considered when seizures are uncontrolled by optimal medical management and when they disrupt the quality of life. Quantifying these issues, however, has defied strict definition, perhaps deservedly, because intractability is clearly more than continued seizures. Only patients know how their lives differ from what they would like them to be; the concept of *disability* includes both physical and psychological components. Some patients with refractory seizures suffer little disability; others, for whatever reason, find their lives severely compromised by infrequent attacks. Still, others have had their seizures completely cured by surgery but are still disabled and incapable of functioning productively. Determining which patients are "medically refractory" and which are "satisfactorily controlled" can always be argued in the abstract.

Fortunately in practice, there is usually general agreement about which patients should be referred for surgical evaluation.

Patients are less likely to benefit from further attempts at medical treatment if seizures have not been controlled after two trials of high-dose monotherapy using two appropriate drugs and one trial of combination therapy. These therapeutic efforts can be accomplished within 1 to 2 years; the detrimental effects of continued seizures or drug toxicity warrant referral to a specialized center after that time.

There are few blanket contraindications to epilepsy surgery today, although patients with severe concurrent medical illness and progressive neurologic syndromes are usually excluded. Some centers prefer not to operate on patients with psychosis or other serious psychiatric disorder, those older than 60 years, and those with an IQ of less than 70. Patients in these categories, however, must be considered individually. Many patients who undergo corpus callosum section for atonic seizures associated with Lennox–Gastaut syndrome have IQs less than 70. Although surgery for epilepsy is increasingly performed in children, functional resections in infancy remain controversial for several reasons: the uncertain natural history of seizures in many of these patients; the unknown effects of surgery on the immature brain; and the lack of data about long-term neurologic, behavioral, and psychological outcomes.

Because of technical advances in imaging and electrophysiologic monitoring, epilepsy surgery is no longer automatically contraindicated in patients with multifocal interictal epileptiform abnormalities or even foci near language or other eloquent cortical areas.

RESECTIVE PROCEDURES

Focal brain resection is the most common type of epilepsy surgery. Resection is appropriate if seizures begin in an identifiable and restricted cortical area, if the surgical excision will encompass all or most of the epileptogenic tissue, and if the resection will not impair neurologic function. These criteria are met most often by patients with temporal lobe epilepsy, but extratemporal resections are increasingly common.

ANTERIOR TEMPORAL LOBE RESECTION

This resective procedure is the most common, but the operation varies in what is considered "standard," especially with regard to how much lateral neocortical and mesial limbic structures are removed. The traditional operation is Spencer's 1991 anteromedial temporal lobe resection, which includes removal of the anterior middle and inferior temporal gyri, parahippocampal gyrus, 3.5 to 4 cm of hippocampus, and a variable amount of amygdala. For nondominant foci, this approach may be slightly modified to include the anterior superior temporal gyrus as well. Increasingly, some centers (including ours) are using selective amygdalohippocampectomy, a smaller resection with similar efficacy. Patients with medial temporal lobe epilepsy associated with hippocampal sclerosis are ideal candidates for either operation because over 80% will become seizure free, with the remainder having substantial improvement. Results of a large multicenter study in the United States were reported by Spencer et al. in 2003, confirming the high rates of complete seizure control following temporal lobe resection [**Level 1**].[11] A randomized controlled Canadian trial has demonstrated clear superiority of surgery over medical management in patients with medial temporal lobe epilepsy [**Level 1**].[12] Other methods of mesial temporal ablation have been reported, including Gamma Knife radiation and localized laser ablation. Although preliminary results are encouraging, it is not known whether these methods are as effective at seizure control as traditional resection or if there are differences in adverse effect outcomes.

Lesionectomy

Well-circumscribed epileptogenic structural lesions (cavernous angiomas, hamartomas, gangliogliomas, and other encapsulated tumors) can be removed by stereotactic microsurgery. The extent to which tissue margins surrounding the lesion are included in the resection depends on how the margins are defined (radiologic, visual, electrophysiologic, or histologic inspection) and the surgeon's preference. Seizures are controlled by this method in 50% to 60% of patients. A lesion involving the cerebral cortex should always be considered the source of a patient's seizures, unless compelling EEG evidence suggests otherwise.

Nonlesional Cortical Resections

When a lesion cannot be visualized by MRI, it is difficult to demonstrate a restricted ictal-onset zone outside the anterior temporal lobe. Although alternative imaging (PET or SPECT scan) may help identify the seizure-onset zone, this situation almost always requires placement of intracranial electrodes to map the extent of epileptogenic tissue and to determine its relation to functional brain areas. Outcome after nonlesional cortical resections is not as good as with anterior temporal lobectomy or lesionectomy, mainly because the boundaries of epileptogenic cortical areas often cannot be delineated precisely, and removal of all the epileptogenic tissue often is not possible.

CORPUS CALLOSOTOMY

Section of the corpus callosum disconnects the two hemispheres and is indicated for treatment of patients with uncontrolled atonic or tonic seizures in the absence of an identifiable focus suitable for resection. Leaving the posterior 20% to 30% of the corpus callosum intact seems to reduce complications. Most patients referred for corpus callosotomy have severe and frequent seizures of multiple types, usually with mental retardation and a severely abnormal EEG (the Lennox–Gastaut syndrome).

Unlike resective surgery, corpus callosotomy is palliative, not curative. Nonetheless, it can be strikingly effective for generalized seizures, with 80% of patients experiencing complete or nearly complete cessation of atonic, tonic, and tonic–clonic attacks. This outcome is often remarkably beneficial because it eliminates falls and the associated self-injury. The effect on partial seizures, however, is inconsistent and unpredictable. Complex partial seizures are reduced or eliminated in about half the patients, but simple or complex partial seizures are exacerbated in about 25%. Therefore, refractory partial seizures alone are not an indication for corpus callosotomy. Similarly, absence, atypical absence, and myoclonic seizures either do not benefit or show an inconsistent response.

HEMISPHERECTOMY

Removal (hemispherectomy) or disconnection (functional hemispherectomy) of large cortical areas from one side of the brain is indicated when the epileptogenic lesion involves most or all of one hemisphere. Because hemispherectomy guarantees permanent hemiplegia, hemisensory loss, and usually hemianopia, it can be considered only in children with a unilateral structural lesion that has already resulted in those abnormalities and who have refractory unilateral seizures. Examples of conditions suitable for hemispherectomy include infantile hemiplegia syndromes, Sturge–Weber disease, Rasmussen syndrome, and severe unilateral developmental anomalies, such as hemimegalencephaly. In appropriate patients, the results are dramatic. Seizures cease, behavior improves, and development accelerates (Table 58.8).

TABLE 58.8 Outcome after Epilepsy Surgical Procedures

Procedure	Seizure Free (%)	Improved (%)	Not Improved (%)	*n*
Anterior temporal lobectomy	69	22	9	3,579
Lesionectomy	67	22	12	293
Nonlesional extratemporal neocortical resection	45	35	20	805
Hemispherectomy	67	21	12	190
Corpus callosum section	8	61	31	563

Modified from Engel J Jr. *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven; 1993.

PREOPERATIVE EVALUATION

The objective in evaluating patients for focal resection is to demonstrate that all seizures originate in a limited cortical area that can be removed safely. This determination requires more extensive evaluation than is necessary in the routine management of patients with epilepsy. The different tests used provide complementary information about normal and epileptic brain functions.

CCTV/EEG monitoring is necessary to record a representative sample of the patient's typical seizures to confirm the diagnosis and classification and also to localize the cortical area involved in ictal onset. Volumetric or other special MRI techniques may demonstrate unilateral hippocampal atrophy or other anatomic abnormalities that may be epileptogenic. PET and ictal SPECT are useful in demonstrating focal abnormalities in glucose metabolism or cerebral blood flow that correspond to the epileptogenic brain region. Neuropsychological testing is useful in demonstrating focal cognitive dysfunction, especially language and memory. Intracarotid injection of amobarbital (the *Wada test*) to determine hemispheric dominance for language and memory competence is generally considered necessary before temporal lobectomy, but the implications of a failed test are uncertain. Although functional MRI (fMRI) reliably lateralizes language, determining memory competence of one temporal lobe has not yet been reliably established.

Intracranial electrodes are necessary if noninvasive methods do not unequivocally localize the epileptogenic area or if different noninvasive tests give conflicting results. Intracranial electrode placement is also necessary when vital brain functions (language, motor cortex) must be mapped in relation to the planned resection.

NEUROSTIMULATION IN DRUG-RESISTANT EPILEPSY

When epilepsy surgery is not possible due to multiple foci of seizure onset or seizure onset in eloquent cortex that is not resectable, neurostimulation has emerged as an alternative to failed drug therapy.

Vagus Nerve Stimulation

This is the first FDA-approved device for the treatment of medically refractory partial seizures. Like corpus callosotomy, vagus nerve stimulation (VNS) is a palliative procedure because very few patients become seizure free. VNS is delivered via a stimulating lead attached to the left vagus nerve. The stimulus generator is implanted in the upper left chest. The device is usually programmed to give a 30-second electrical pulse every 5 minutes, although stimulus parameters can be adjusted to the requirements of an individual patient. In patients with aura, a magnetic wand can be used to deliver VNS on demand, which may abort seizure progression. About 55% of children have at least a 50% reduction in seizure frequency, which compares favorably with the efficacy of new AEDs [**Level 1**].[13] VNS may be considered for seizures in children, for Lennox Gastaut associated seizures, and for improving mood in adults with epilepsy (Level C). VNS may be considered to have improved efficacy over time. Children should be carefully monitored for site infection after VNS implantation. Chronic adverse effects include hoarseness and difficulty swallowing, both of which increase at the time of stimulation.

Because VNS became FDA approved, several other therapies using neurostimulation have been developed, including responsive neurostimulation, deep brain stimulation of the anterior nucleus of the thalamus, trigeminal nerve stimulation, and transcutaneous VNS.

Deep Brain Stimulation

The anterior nucleus of the thalamus, a core component of the Papez circuit, serves as a relay station that can amplify and synchronize seizure discharges from the hippocampus and the thalamus. Therefore, its inhibition by electrical stimulation is thought to abort or prevent seizures. Multicontact depth electrodes are implanted bilaterally into the anterior nuclei using a stereotactic approach. In the pivotal DBS study, depression (14.8% in active treatment vs. 1.8% in controls) and memory impairment (13% in active treatment vs. 1.8% in controls) were the most common adverse events. Asymptomatic hemorrhages occurred in 4.5% of subjects, but no disability or death was attributed to the hemorrhages.

Responsive Neurostimulation

The responsive neurostimulation (RNS) is now FDA approved as of November 2013 and commercially available as the NeuroPace device for individuals 18 years of age or older with drug-resistant epilepsy and partial-onset seizures that localize to no more than two epileptogenic foci. The NeuroPace responsive neurostimulation system consists of a pulse generator, seizure detection software, and recording and stimulating intracranial electrodes. Unlike the other systems described earlier which deliver a preprogrammed stimulation to prevent seizures, the RNS system works by detecting a seizure and then delivering a stimulus to terminate the electrical component of the seizure at its point of origin. In the pivotal trial which was randomized, prospective, double-blind, sham stimulation controlled, there was no difference in the rate of adverse events between the active and sham stimulation groups. However, the study demonstrated that patients with the device turned on had a 38% reduction in the average number of seizures per month,

compared to a 17% reduction in the sham group. The depth or subdural strip electrodes are placed in close proximity to the seizure focus that is predetermined by surface/depth electrode video EEG evaluation. Hence, patients who are a high surgical risk cannot receive this device.

Once the device is implanted, patients cannot have an MRI, electroconvulsive therapy, transcranial magnetic stimulation, and diathermy procedures. Status epilepticus is covered in Section II, Chapter 6.

GENE MUTATIONS IN EPILEPSY

Genetic factors are implicated strongly in several epilepsy syndromes, and twin studies have confirmed important genetic determinants in both localization-related and generalized types of seizure disorders. The concordance rate for monozygotic twins with idiopathic generalized epilepsy is well over 75%. Hereditary aspects are easiest to discern in childhood absence epilepsy, JME, benign rolandic epilepsy, and idiopathic grand mal seizures. Some inherited disorders, such as tuberous sclerosis and neurofibromatosis, are associated with brain lesions that in turn give rise to symptomatic epilepsies. In most cases of epilepsy, however, the role of genetic factors is complex because there are multiple interacting genes that convey varying degrees of seizure susceptibility and also affect the brain's response to environmental influences. In any given patient, the relative contribution from genetic or acquired factors determines whether the epilepsy presents as an idiopathic syndrome or as a symptomatic disorder. In addition, however, there also seems to be some degree of sharing of genetic susceptibilities in both the idiopathic and symptomatic epilepsies because children of parents with either localization-related or generalized epilepsy develop seizures at increased rates, although the difference is greatest in families with idiopathic generalized epilepsy. Thus, a major challenge facing investigators today is to clarify how different genes alter an individual's susceptibility to seizures and epilepsy in the presence of acquired brain pathology or as a reaction to acute or subacute cerebral dysfunction. This is no easy task, however, because the number of genes that encode molecules that regulate cortical excitability directly through membrane and synaptic functions and the second messenger cascades that indirectly regulate membrane proteins involved in signal transduction is very large.

A number of causative genes have been identified in idiopathic epilepsies with a monogenic mode of inheritance (Table 58.9). Mutations in two voltage-gated potassium channel genes, *KCNQ2* (chr 20q13) and *KCNQ3*, (chr 8q24), cause benign familial neonatal convulsions. Autosomal dominant frontal lobe epilepsy is caused by mutations in two cholinergic receptor genes, the *CHRNA4* (chr 20q13) and *CHRNB2* (chr 1q). A syndrome of generalized epilepsy with febrile seizures ($GEFS^+$) has been related to mutations in three Na^+ channel subunits: *SCN1B* (chr 19q13), *SCN1A* (2q24), and *SCN2A* (2q24). A similar syndrome has also been seen in families with mutations in the $\gamma 2$ subunit gene (*GABRG2* on chr 5q34) of the $GABA_A$ receptor. De novo mutations in the $\alpha 1$ subunit of the Na^+ channel also cause severe myoclonic epilepsy of infancy (Dravet syndrome). Mutations in the *CLCN2* gene encoding a Cl^- channel have recently been described in three families with idiopathic generalized epilepsies of heterogeneous phenotype. An autosomal dominant form of JME occurring in a French Canadian family is associated with a mutation in the $\alpha 1$ subunit of the GABA receptor (*GABRA1*). A mutation in the leucine-rich glioma inactivated (*LCI1*) gene on chromosome 10q22-24 causes an autosomal dominant form of partial epilepsy with auditory features.

TABLE 58.9 Genes Identified in Idiopathic Human Epilepsies

Gene	Syndrome	Chromosome
Na^+ Channels		
SCN1A	Generalized epilepsy with febrile seizures plus ($GEFS^+$)	2q24
SCN1A	Severe myoclonic epilepsy of infancy	2q
SCN2A	Benign familial neonatal seizures and $GEFS^+$	2q24
SCN1B	$GEFS^+$	19q13
K^+ Channels		
KCNQ2	Benign familial neonatal seizures	20q13
KCNQ3	Benign familial neonatal seizures	8q24
Cl^- Channels		
CLN2	Idiopathic generalized epilepsy (heterogeneous)	3q26
Ca^{2+} Channels		
CACNA1A (P/Q)	Absence epilepsy and cerebellar ataxia	19q
CACNB4	Idiopathic generalized epilepsy (heterogeneous)	2q22–23
Nicotinic AChR		
CHRNA4	Autosomal dominant nocturnal frontal lobe epilepsy	20q13
CHRNB2	Autosomal dominant nocturnal frontal lobe epilepsy	1q
$GABA_A$ Receptor		
GABRG2	$GEFS^+$	5q34
GABRA1	Juvenile myoclonic epilepsy (French Canadian family)	
Other		
LGI1	Autosomal dominant partial epilepsy with auditory features	10q22–24

AChR, acetylcholine receptor; GABA, γ-aminobutyric acid.

PSYCHOSOCIAL AND PSYCHIATRIC ISSUES

The impact of epilepsy on the quality of life is usually greater than the limitations imposed by the seizures alone. The diagnosis of epilepsy frequently carries other consequences that can greatly alter the lives of many patients. For adults, the most important problems are discrimination at work and driving restrictions, which lead to loss of mobility and independence. Children and adults alike may be shunned by uninformed friends. Patients must learn to avoid situations that precipitate seizures, and a change in lifestyle may be necessary. Common factors that increase the likelihood of seizure occurrence include sleep deprivation (whether due to lifestyle

TABLE 58.10 Factors that Lower the Seizure Threshold

Common	Occasional
Sleep deprivation	Barbiturate withdrawal
Alcohol withdrawal	Hyperventilation
Stress	Flashing lights
Dehydration	Diet and missed meals
Drugs and drug interactions	Specific "reflex" triggers
Systemic infection	
Trauma	
Malnutrition	
Noncompliance	

or to coexisting sleep disorders), alcohol (and other drugs), and emotional stress (Table 58.10). Compliance with AED treatment is often an issue, especially with adolescents. Psychiatric symptoms, especially depression, may complicate management.

Some restrictions are medically appropriate, at least for limited times. For example, when seizures impair consciousness or judgment, driving and certain kinds of employment (working at exposed heights or with power equipment) and a few other activities (swimming alone) should be interdicted. On the other hand, legal prohibitions on driving vary in different states in the United States and in different countries and are often not medically justified. Employers frequently have unrealistic fears about the physical effects of a seizure, the potential for liability, and the impact on insurance costs. In fact, the Americans with Disabilities Act prohibits denying employment to persons with disability if the disability does not prevent them from meeting job requirements.

Children have special problems because their seizures affect the entire family. Parents may, with the best of intentions, handicap the child by being overly restrictive. The necessary and special attention received by the "sick" child may encourage passive manipulative behavior and overdependence while unintentionally exacerbating normal sibling rivalries.

The physician must be sensitive to these important quality of life concerns, even when they are not raised spontaneously by the patient or family. In fact, psychosocial issues often become the major focus of follow-up visits after the diagnosis has been made, the initial evaluation completed, and treatment started. We cannot emphasize too much the physician's responsibility to educate society to counter misperceptions and prejudices and to separate myth from medical fact. The Epilepsy Foundation (Landover, MD; 1-800-332-1000; www.epilepsyfoundation.com) and its nationwide system of affiliates have a wealth of materials about epilepsy suitable for patient, family, and public education.

Depression is common in people with epilepsy: Over half of patients with uncontrolled seizures are depressed. Even patients with well-controlled seizures have higher rates of depression than the general population. Suicide rates are tripled, with the highest rates seen in the 6 months after diagnosis. Patients should be observed for signs of depression and queried specifically about their mood, with attention to the potential need for psychiatric referral and initiation of antidepressant drugs. A simple screening tool developed specifically for use in people with epilepsy appears to allow rapid and accurate recognition of major depression. The FDA recently released an advisory indicating an increased risk of suicidal thoughts in patients enrolled in clinical trials (0.43% in patients adding any additional agent vs. 0.22% for those adding placebo). The significance for newly diagnosed patients is unclear, but it seems prudent to observe patients starting new AEDs closely for mood changes.

Treatment of depression begins with optimal treatment of the seizure disorder. Barbiturate and succinimide drugs may adversely affect mood, inducing symptoms that mimic endogenous depression. Topiramate and levetiracetam seem to cause depression in a small minority of patients, whereas lamotrigine can occasionally improve depression. Levetiracetam has also been associated with rare psychosis. Although tricyclic antidepressants reduce the seizure threshold in experimental models of epilepsy, this is not a practical concern because they only rarely trigger seizures or increase seizure frequency in humans. Monoamine oxidase (MAO) inhibitors neither induce seizures nor increase seizure frequency. Modern electroconvulsive therapy does not worsen epilepsy. We have used all available selective serotonin reuptake inhibitors (SSRIs) without exacerbating seizures.

Anxiety disorders are also common in epilepsy patients. When present, some AEDs can exacerbate the condition, mainly levetiracetam, topiramate, and zonisamide. Other agents (including gabapentin, pregabalin, and benzodiazepines) can improve anxiety. Of the benzodiazepines, only clonazepam and clobazam are used for chronic treatment of epilepsy.

The relation between psychosis and epilepsy is controversial. No convincing evidence shows that interictal psychosis is a manifestation of epilepsy, but some demographic features are overrepresented in patients with epilepsy. Postictal psychosis is, however, a well-recognized and self-limited complication of epilepsy. Its cause is unknown, but it may represent a behavioral analog of Todd paresis. Symptoms typically appear 24 to 72 hours after a lucid interval following a prolonged seizure or cluster of seizures and are more common in patients with a history of encephalitis or a family history of neuropsychiatric problems. Postictal psychosis is more common with ambiguous localization on monitoring suggesting that broad, bilaterally distributed epileptogenic networks may be a risk factor. Delusions and paranoia are common. The psychosis is self-limited, usually to a few days, although symptoms occasionally last as long as 1 to 2 weeks. Treatment with haloperidol or risperidone is usually effective. In cases where postictal psychosis regularly follows clusters of seizures, chronic treatment with low-dose risperidone can be helpful. Long-term emphasis should be on improving seizure control. Phenothiazines, butyrophenones, and clozapine lower seizure threshold in experimental animals and occasionally seem to induce seizures in nonepileptic patients. Most occurrences have been associated with high drug doses or a rapid increase in dose. With the possible exception of clozapine, however, little evidence supports the notion that reasonable and conservative use of antipsychotic medications increases seizure frequency in patients with epilepsy.

Interictal aggressive behavior is not more common in people with epilepsy. Directed aggression during seizures occurs in less than 0.02% of patients with severe epilepsy; it is almost certainly less common in the general epilepsy population. Undirected pushing or resistance occasionally occur postictally when attempts are made to restrain confused patients.

COMPLIANCE

The most common cause of breakthrough seizures is noncompliance with the prescribed therapeutic regimen. Only about 70% of patients take antiepileptic medications as prescribed. For

phenytoin or carbamazepine, noncompliance can be inferred when sequential blood levels vary by more than 20%, assuming similarly timed samples and unchanged dosage. Persistently low AED levels in the face of increasing dosage also generally imply poor compliance. Caution is warranted with phenytoin, however, because as many as 20% of patients have low levels as a result of poor absorption or rapid metabolism.

Noncompliance is especially common in adolescents and elderly persons, when seizures are infrequent or not perceived as disabling, when AEDs must be taken several times each day, and when toxic effects persist. Compliance can be improved by patient education, by simplifying drug regimens (using less frequent dosing with extended-release preparations when appropriate), and by tailoring dosing schedules to the patient's daily routines. Pillbox devices that alert the patient to scheduled doses can be useful.

PSYCHOGENIC SEIZURES

Psychogenic nonepileptic seizures (PNES) are diagnosed in 20% to 30% of patients who present to epilepsy centers for difficult to control seizures. They are often misdiagnosed as epileptic seizures and are treated with antiseizure medications without adequate investigation, quite often resulting in significant morbidity. The estimates of prevalence of concurrent epilepsy among patients with PNES vary from 5% to 56%. They are believed to be a manifestation of an underlying psychological stress and are classified under conversion disorders, which are a type of somatoform disorder. A specific traumatic event at any point of time in the patient's life, including physical or sexual abuse, death of a loved one, divorce, or other similar loss may be identified in patients with PNES. The diagnosis of PNES can be challenging, as the presentation of these seizures is very diverse; they can range from mimicking a generalized convulsion to less often, an atonic event. Although no single semiologic feature is specific for diagnosing PNES, the motor manifestations usually are more asynchronous, variable, and fluctuating in intensity, and specific movements such as writing, thrashing, pelvic thrusting, opisthotonus, and jactitation are more suggestive of PNES (Video 58.6). Ictal stuttering, weeping, and eye closure are relatively uncommon in epileptic seizures and are suggestive of, but not diagnostic of, PNES. In one study, the occurrence of an episode in the doctor's examination room was estimated to have a 75% predictive value for PNES. Video-EEG evaluation is almost always required to verify the diagnosis, as descriptions of patients and onlookers are invariably incomplete, and even trained medical personnel cannot reliably distinguish epileptic from nonepileptic seizures by visualization alone. PNES also can occur in patients with concurrent epilepsy, further confounding accurate diagnosis of each event. Even with video-EEG recording, some frontal lobe seizures with bizarre semiologies can be misdiagnosed as PNES and often do not have an ictal EEG correlate. The key challenge is in presenting the diagnosis to patients, as acceptance of the diagnosis is a very important factor in response to treatment and counseling. Psychiatric intervention is the mainstay of treating PNES and is individualized according to the underlying psychiatric comorbidity. Ideally after diagnosis, the patients should be followed by a neurologist and a psychiatrist with close dialogue between the two, and cautious discontinuation of the antiseizure medication should be coordinated, where applicable. Neurologic follow-up should be maintained after the diagnosis, until the patient has been fully transitioned to psychiatric care.

Videos can be found in the companion e-book edition. For a full list of video legends, please see the front matter.

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