



G. ARUNKUMAR, MD

Department of Neurology,
Cleveland Clinic

HAROLD MORRIS, MD

Department of Neurology,
Cleveland Clinic

Epilepsy update: New medical and surgical treatment options

■ ABSTRACT

A variety of new drugs and surgical options are available for the treatment of epilepsy. Yet the cornerstone of therapy remains the appropriate classification of different types of seizures. This review explores the current knowledge about this common neurological problem and presents an outline for making the diagnosis, controlling the seizures, and preserving quality of life.

■ KEY POINTS

A single seizure should not automatically lead to a diagnosis of epilepsy.

Several conditions, such as arrhythmias, narcolepsy, and transient ischemic attacks, are commonly mistaken for epilepsy.

Up to 75% of patients can achieve seizure control with monotherapy. However, antiepileptic drugs must be chosen on the basis of their efficacy against a particular seizure type.

Surgery is an option for medically refractory epilepsy, although careful patient selection is crucial for success.

IN TREATING EPILEPTIC SEIZURES, physicians have more diagnostic and treatment options than ever before. There are a variety of new drugs available to treat epilepsy, and surgery has been refined to the point that it is a reasonable option for the patient with refractory seizures.

With so many options available, it remains crucial that epilepsy be properly diagnosed and the type of seizure identified, as treatment is guided by these determinations. Those clinical decisions are based on answering a series of questions from the patient's history.

■ DID THE PATIENT HAVE A SEIZURE?

Any paroxysmal event that transiently alters neurologic function can be mistaken for an epileptic seizure. Therefore, the differential diagnosis includes the following:

Cardiac arrhythmias, vasovagal syncope, and postural hypotension can produce loss of consciousness and result in brief generalized clonic movements, if cerebral hypoxia is prolonged.

Narcolepsy may be mistaken for a seizure disorder, and cataplexy may mimic atonic seizure.

Parasomnias (sleepwalking, night terror) may be difficult to differentiate from nocturnal seizures.

Complicated migraine can mimic focal sensory seizures or present as an acute confusional state resembling absence seizure or complex partial status epilepticus.

Transient ischemic attacks presenting with brief, repetitive, stereotyped sensory or

TABLE 1

Classification of epileptic seizures

Generalized seizures

- Convulsive
 - Tonic-clonic
 - Clonic-tonic-clonic
 - Tonic
 - Clonic
 - Myoclonic
 - Atonic
- Nonconvulsive
 - Absence
 - Atypical absence

Partial seizures (focal, local)

- Simple partial seizures (consciousness not impaired)
- Complex partial seizures (consciousness impaired)
- Partial seizures evolving to generalized tonic-clonic seizures

Unclassified seizures

motor deficits, amnesia, or aphasia can be hard to differentiate from simple partial seizures.

Transient global amnesia can produce sudden confusion and acute loss of memory. Cognitive function and language remain intact, and these attacks rarely recur.

Pseudoseizures are suggested by bizarre facial grimacing, body posturing, opisthotonus, pelvic thrusting, and completely asynchronous thrashing of limbs. They are most common in patients with a history of sexual, physical, or substance abuse, personality disorder, or other psychiatric illness. Patients with pseudoseizures can also have a real seizure disorder, and videoencephalographic monitoring may be required to make the diagnosis.

■ WHAT TYPE OF SEIZURE DID THE PATIENT HAVE?

This question is more than academic, since the choice of drug to use, if any, depends on the type of seizure. The current classification system divides seizures into two major types: generalized and partial (TABLE 1).¹

Generalized seizures

Generalized seizures begin diffusely in the brain and involve both cerebral hemispheres simultaneously from the onset. They are subdivided mainly on the basis of the ictal signs and symptoms.

Generalized tonic-clonic seizures (formerly known as grand mal seizures) are common in both children and adults, and account for approximately 25% of seizures encountered.²

Usually, the seizure begins with a tonic phase: the patient abruptly loses consciousness and rigidly extends all four limbs and trunk. He or she may cry out, as air is forcefully expelled across contracted vocal cords. The tonic phase usually lasts about 20 seconds, and is followed by a clonic phase, with bilaterally synchronous muscle jerking. Less often the sequence differs, a clonic phase preceding the tonic phase (clonic-tonic-clonic seizure); in other patients, only a tonic or clonic phase is seen. Urinary incontinence is common. The entire seizure does not usually last more than 90 seconds.

After the seizure, patients are briefly unarousable, lethargic, and confused. With recovery, the patient may complain of headache, muscle tenderness, a sore bitten tongue, or mood changes lasting up to 24 hours.

Generalized tonic-clonic seizures occur in a number of epileptic syndromes, both idiopathic and symptomatic (secondary).³ They can also occur in isolation or along with other central nervous system disorders (eg, stroke, intracranial hemorrhage, meningoencephalitis, or brain tumor), systemic disturbances affecting fluid and electrolyte balance, or hepatic or renal failure. The prognosis depends on the etiology.

Absence seizures (formerly known as petit mal seizures) also begin abruptly. Without warning, the patient stops what he or she is doing and stares, motionless, off into space, experiencing a brief impairment or loss of consciousness. In addition, he or she may show mild clonic or rhythmic blinking of eyelids, an increase or decrease in postural tone, automatisms such as lip-smacking, swallowing, or fumbling with clothes (especially if absences last longer than 10 seconds), and autonomic signs such as facial pallor, mydriasis, and piloerection.

Absence seizures usually last less than 10 seconds, rarely as long as 1 minute. Afterward, there is no postictal confusion. Atypical absence seizures are usually associated with mental retardation and neurological abnormalities such as Lennox-Gastaut syndrome.

Suspect a pseudoseizure if the signs are bizarre



Myoclonic seizures are very brief, sudden muscle jerks that can occur bilaterally (synchronously or asynchronously) or unilaterally. Total loss of awareness is uncommon, but myoclonic seizures may cluster, climaxing in a generalized tonic-clonic seizure with loss of consciousness. Myoclonic seizures often occur while the patient is falling asleep or awakening. However, many people without epilepsy also experience myoclonus while going to sleep. The jerks in epileptic myoclonus occur concurrently with an ictal electroencephalographic discharge.

Atonic seizures. In this type of seizure, the patient abruptly loses muscle tone and falls to the floor. Alternatively, only the head may drop. Consciousness is impaired, but only briefly. If a brief myoclonic seizure or tonic spasm precedes the atonic seizure, the combination adds an accelerated force to the fall, contributing to a high rate of self-injury.

Partial seizures

Partial or focal seizures are limited at onset to a part of one cerebral hemisphere. The most important subdivision is based on consciousness, which is preserved in simple partial seizures but impaired in complex partial seizures.

Simple partial seizures occur when ictal discharges remain restricted to a circumscribed area of the cortex. The patient remains conscious during the seizure. Subjective sensory and psychoillusionary phenomena (auras) occur in about 60% of patients with focal seizures. Focal motor seizures may remain strictly focal, or they may spread to adjacent cortical areas, producing a sequential involvement of body parts known as a Jacksonian seizure. Versive seizures—forceful, sustained deviations of head and eyes—occur on the side opposite to the discharge. Somatosensory seizures consist of localized numbness, paresthesia, vertigo, and auditory and visual hallucinations.

Complex partial seizures are characterized by impaired consciousness, unresponsiveness, and automatic behavior, and are often followed by postictal confusion. They may begin with arrest of ongoing behavioral activity or a motionless stare,^{4,5} and they may or may not be preceded by a simple partial

seizure. Most complex partial seizures originate in the temporal lobe, particularly the mesial basal region. Remaining cases arise mainly from the frontal lobe, with lesser numbers originating in the parietal and occipital lobes. Complex partial seizures that arise in the frontal lobes tend to be brief, may occur several times per day, and begin and end abruptly. Patients may remain conscious and exhibit complex, bizarre motor manifestations such as thrashing of arms, pelvic thrusting, pedaling leg movements, and loud vocalization, all of which might suggest nonepileptic seizures. This type of seizure accounts for 50% of seizures in adults.

■ IS THERE AN IDENTIFIABLE CAUSE OF THE SEIZURE?

Not all seizures imply epilepsy, although a diagnosis of epilepsy requires the presence of seizures. Seizures may occur during the course of an acute medical or neurological illness and may not persist after the underlying disorder has resolved. Systemically ill patients with isolated seizures have a lower seizure threshold and may not require long-term treatment with anticonvulsant drugs if the underlying cause of the seizures can be corrected.

Fever

Febrile seizures occur in 3% of children between the ages of 6 months and 4 years. Because febrile seizures are an acute sign of an illness, they should not be labelled as epilepsy, even if they recur.

Febrile seizures are categorized as simple or complex. Simple febrile seizures are solitary events lasting less than 15 minutes and lacking focal signs. Complex febrile seizures have a focal onset, are prolonged (> 15 minutes), and occur repeatedly within 24 hours.

The diagnosis is made by excluding other causes such as meningitis, metabolic abnormalities, or structural brain lesions. Lumbar puncture is essential to exclude meningitis, since nuchal rigidity and Brudzinski's sign are not reliable in young infants.

About 30% of children with febrile seizures have a second attack.^{8,9} Recurrences are more likely if the first febrile seizure occurs before the age of 1 year, if there is a

Do not label febrile seizures as epilepsy, even if they recur

Seizures during pregnancy

A PPROXIMATELY 30% OF WOMEN with epilepsy have an increase in seizure frequency during pregnancy. Poor seizure control may be related to increased hepatic and renal clearance of antiepileptic drugs, alteration of plasma protein binding, increased volume of distribution, malabsorption, noncompliance, or hormonal effects. Free antiepileptic drug levels should be monitored monthly and the dosage adjusted.

There is no drug of first choice for seizures in pregnancy. The risk of major fetal malformations such as cardiac and neural tube defects is 4% to 6%, which is twice that in children of nonepileptic women. With valproate use, the prevalence of neural tube defects is 1% to 2%; with carba-

mazepine it is 0.5%.^{6,7} Use of polypharmacy carries a 10% risk of major fetal malformation. It is best to avoid valproate and carbamazepine in women with a family history of neural tube defects, but if these drugs are used, ultrasound evaluation and amniocentesis at 18 to 19 weeks of pregnancy have a 95% accuracy in detecting neural tube defects.

The risk of neural tube defects may be reduced by using folic acid (1 mg/day) before conceiving, and by using a single antiepileptic drug in the lowest effective dose throughout pregnancy. In addition, oral vitamin K (20 mg/day) during the last month of pregnancy can prevent hemorrhagic diathesis in the newborn.

family history of febrile seizures, if the seizure occurred in the first hour of fever, or if the seizure occurred at a temperature < 101°F. The incidence of epilepsy increases to about 10% in children with complex febrile seizures, a family history of epilepsy, or who were neurodevelopmentally abnormal.

Although both phenobarbital and valproate reduce recurrent seizures, evidence does not show that they reduce the risk of developing epilepsy later on. Treatment should be reserved for children with complex febrile seizures who are developmentally abnormal or have a strong family history of epilepsy. A reasonable alternative is to give diazepam rectally during febrile illnesses to reduce seizure recurrence.¹⁰

Drug-induced seizures

Many medications increase the risk of seizures, but the mechanisms are poorly understood. Patients with epilepsy, underlying neurologic dysfunction, reduced drug elimination, and breakdown of the blood-brain barrier are at increased risk for drug-induced seizures. Antipsychotics, theophylline, tricyclic antidepressants, meperidine, cyclosporine, cisplatin, and beta-lactam antibiotics can cause seizures at therapeutic doses. The convulsant effects of lidocaine, aminophylline, isoniazid, and lithium are dose-related. Monoamine oxidase

inhibitors, alprazolam, and trazodone do not cause seizures. Withdrawal of benzodiazepines, barbiturates, baclofen, and alcohol is another important cause of seizures.

Trauma

Seizures can occur immediately (within hours), early (< 1 week), or late (> 1 week) after trauma to the head. Immediate and early seizures result from acute reaction of the brain to trauma. Late seizures are more likely after missile wounds that penetrate the dura, depressed skull fractures, cerebral hematomas, injury in a central-parietal location, prolonged post-traumatic amnesia, fixed neurological deficits, and early seizures.^{11,12} Patients with early seizures and severe head trauma should receive anticonvulsant treatment. In the absence of overt seizures, the anticonvulsant should be discontinued after 4 weeks, as available data indicate that antiepileptic drugs do not prevent late epilepsy.

■ WHAT EVALUATION IS NECESSARY?

A careful history is the single most important part of the diagnostic evaluation, and should include the birth history, developmental milestones, past history of febrile seizures, CNS infections, head trauma, alcohol and substance abuse, and family history of epilepsy. In addition:

Avoid using multiple antiepileptic drugs in pregnant women



Status epilepticus: A medical emergency

IN STATUS EPILEPTICUS (SE), seizures recur repeatedly, and cerebral function does not recover fully between seizures. Another definition: more-or-less continuous clinical or electrical seizure activity lasting more than 30 minutes, whether or not consciousness is impaired. More than 50% of patients who develop SE have no history of epilepsy, and 10% of patients who develop epilepsy present with SE.

Complications of SE include death, fractures, myoglobinuria with renal shutdown, cardiotoxicity, pulmonary edema, and fixed neurologic deficits or epilepsy.

Classification of status epilepticus

SE is classified as:

Generalized convulsive SE (tonic-clonic, tonic, clonic, myoclonic, subtle). Generalized tonic-clonic SE is a major medical and neurologic emergency that produces a high rate of mortality. It may manifest as either overt generalized tonic-clonic seizures or subtle generalized convulsive SE, in which the patient is in a profound stupor or coma, exhibits repetitive rhythmic subtle motor convulsive activity, and shows bilateral ictal activity on the EEG.

Nonconvulsive SE (absence, complex partial). Patients with nonconvulsive SE are described as being in a "fugue" state with various degrees of impaired consciousness and automatic behavior. Nonconvulsive SE may be difficult to distinguish from intoxication, encephalopathy, or a psychiatric disturbance and presents a diagnostic challenge.

Simple partial SE (motor [epilepsia partialis continua], sensory, aphasic).

Causes of status epilepticus

Noncompliance with anticonvulsant medication is an important cause of SE in epileptic patients. In patients without epilepsy, the causes of SE include alcohol withdrawal, acute intracerebral events such as stroke and intracerebral hemorrhage, cen-

tral nervous system infections, neoplasms, drug intoxication, anoxic encephalopathy, and acute metabolic derangements. Abuse of cocaine, phenylcyclidine, or amphetamine can also provoke SE.

Treatment of status epilepticus

SE is a medical emergency that requires management in an intensive care unit with close monitoring. Time is critical, as the morbidity and mortality rates increase with duration of seizure activity. Treatment consists of stabilizing vital physiologic functions, administering 100 mg of thiamine followed by 50 mL of 50% glucose if hypoglycemia is suspected, and starting intravenous antiepileptic medications. Status epilepticus may result from alcohol withdrawal, and thiamine prevents the development of Wernicke's encephalopathy.

Diazepam, lorazepam, fosphenytoin, and phenobarbital are all effective in managing generalized convulsive SE. Treiman¹³ found that lorazepam was effective in 78% of cases in which it was used as the first drug, compared with 49% of cases treated initially with phenytoin. Therefore, we recommend starting with lorazepam, in a dose of 0.1 mg/kg at 2 mg/minute to a total dose of 8 mg.

If lorazepam fails to stop the SE, then fosphenytoin should be given in a loading dose of 20 mg/kg. If SE persists, the initial dose may be followed by additional doses of 10 mg/kg. Because hypotension frequently occurs in elderly, severely ill patients with prolonged SE, it may be necessary to slow the rate of infusion or consider dopamine or other pressor agents.

If SE still persists, an endotracheal tube should be inserted for respiratory support and phenobarbital (20 mg/kg) started at a rate of 50 to 100 mg/minute. In refractory SE, pentobarbital coma may be required. SE appears to be more difficult to control the longer it persists, and also with certain underlying conditions such as anoxia, cerebrovascular accident, or tumor.

A physical and neurological examination may help uncover a localized cerebral pathology.

A metabolic and toxic screen should be

obtained to exclude systemic disease and substance abuse.

Holter monitoring may be necessary in patients with a history of cardiac arrhythmias.

TABLE 2

Choice of antiepileptic drugs

SEIZURE TYPE	FIRST CHOICE	SECOND CHOICE
Primary generalized seizures		
Tonic-clonic	Carbamazepine Phenytoin Valproate	Lamotrigine Phenobarbital Primidone
Tonic, clonic, atonic	Valproate	Lamotrigine Phenobarbital
Absence	Ethosuximide Valproate	Lamotrigine
Myoclonic	Clonazepam Valproate	Lamotrigine Phenobarbital
Partial seizures (all types)	Carbamazepine Phenytoin Valproate	Gabapentin Lamotrigine Phenobarbital Primidone

The choice of drug depends on the type of seizure

Lumbar puncture is mandatory in acute cases if meningitis or encephalitis is suspected.

Electroencephalography (EEG) is essential for establishing the diagnosis, classifying seizures, identifying epileptic syndromes, and making therapeutic decisions. The sensitivity of a single EEG recording for identifying epileptiform abnormalities is about 50%, increasing to 90% with the third recording.

Magnetic resonance imaging (MRI) should be done in all patients who have symptomatic partial or symptomatic generalized epilepsy. MRI can readily reveal cortical dysplasia, hippocampal sclerosis, cavernous malformations, gliomas, and gangliogliomas, which may be missed on computed tomography.

Functional neuroimaging with positron-emission tomography and single-photon emission computed tomography are useful only for presurgical evaluation.

■ IS DRUG THERAPY NEEDED?

Whether to prescribe an antiepileptic drug after a first seizure is controversial. Overall, the risk of recurrence after a first unprovoked seizure is 14% within 1 year and 34% within 5 years.¹⁴ The risk is much higher if the seizure is focal in onset or if MRI shows a lesion, EEG

demonstrates epileptiform activity, or the patient has focal neurological deficits. Drug treatment causes adverse effects in approximately 30% in the first few months.

A large multicenter study from Italy demonstrated that antiepileptic drugs reduced the risk of relapse after the first unprovoked generalized tonic-clonic seizure. No information is available whether early treatment reduces the severity of epilepsy or increases the chances of prolonged remission. Patients are at low risk of further seizures if they have a normal EEG, normal physical findings, normal brain imaging, no history of cerebral injury, and no family history of epilepsy. The decision to treat should be made only in consultation with the patient after weighing the unique circumstances posed by that individual.

■ STARTING AN ANTIEPILEPTIC DRUG

A complete blood count (including a differential white cell count and platelet count), serum chemistry, and liver function tests should be performed at baseline and 6 to 8 weeks after antiepileptic drug therapy has been started. However, a routine schedule of laboratory monitoring will not detect or prevent severe idiosyncratic reactions. The patient should be familiar with short-term and long-term adverse effects, especially the early warning signs of idiosyncratic reactions, such as dermatologic reactions and aplastic anemia. Repeat laboratory monitoring is indicated if symptoms of adverse effects develop.

Antiepileptic drugs are selected on the basis of their efficacy against a particular seizure type (TABLE 2), potential side effects, ease of administration, safety, and cost. Overall, up to 75% of patients can achieve seizure control taking one drug alone.

The agent should be started at a low dose and gradually increased until adequate control is achieved or intolerable adverse effects occur. Dosage changes (TABLE 3) generally should not be made until the effects of the drug have been observed at steady-state concentrations (five drug half-lives). Dosage intervals should be equal to the half-life to minimize fluctuations between peak and trough blood concentrations. Blood levels are

TABLE 3

Antiepileptic drugs—pharmacokinetics and dosage

MEDICATION	HALF-LIFE (HOURS)	METABOLISM	PROTEIN BINDING (%)	ADULT DOSE (MG/DAY)	PEDIATRIC DOSE (MG/KG/DAY)
Phenytoin	24*	Hepatic	85–90	200–500	4–7
Carbamazepine	12†	Hepatic	60–70	600–1,600	5–20
Valproate	10	Hepatic	70–90	1,000–3,000	10–15
Phenobarbital	96	Hepatic	45–50	90–180	2–6
Primidone‡	12	Hepatic	< 30	300–1,500	10–20
Ethosuximide	36	Hepatic	< 10	750–1,500	15–40
Fosphenytoin	8–17 min	Hepatic	85–90	See below§	See below§
Gabapentin	6–8	Renal	Negligible	900–4,800	10–30
Lamotrigine	24	Hepatic	55	200–700	5–15
Topiramate	18–24	Renal	< 15	200–800	1–9
Vigabatrin	5–7	Renal	Negligible	2,000–4,000	50–150
Tiagabine	7	Hepatic	95	32	0.25–1.5

*Phenytoin has nonlinear kinetics

†Carbamazepine induces its own metabolism

‡Primidone's primary metabolites, phenobarbital and phenylethylmalonamide, are pharmacologically active; values given are for the parent compound

§Loading dose in status epilepticus: 15–20 mg/kg intravenously at 150 mg/minute in adults or 2–3 mg/kg/minute in children weighing < 50 kg; maintenance dose: 4–7 mg/kg intramuscularly or intravenously at 150 mg/minute in adults or 2–3 mg/kg/minute in children < 50 kg twice daily

||Lamotrigine's half-life is affected by other antiepileptic drugs

||Not FDA-approved in children

Start with a low dose and increase it slowly

useful in achieving optimal therapy, but they should never be the goal of treatment. Some patients tolerate drug levels 50% higher than the therapeutic limit, while others experience adverse reactions at subtherapeutic levels. Polypharmacy should be used only if monotherapy with first-choice drugs fails.

STANDARD ANTIEPILEPTIC DRUGS

Phenytoin

Pharmacokinetics. Phenytoin exhibits nonlinear kinetics at therapeutically useful serum concentrations, ie, a small change in dosage can result in a large change in serum concentration. Therefore, this drug requires cautious titration, using dose increments of 30 mg to avoid toxic effects.

Interactions. Phenytoin is a potent

enzyme-inducer and may decrease the effectiveness of oral anticoagulants, certain antibiotics (doxycycline, rifampicin), oral contraceptives, cyclosporine, corticosteroids, theophylline, and antiarrhythmic agents (disopyramide, mexiletine, quinidine).

Adverse effects. Skin eruptions occur in 8% of patients, and mild gingival hyperplasia and hirsutism occur in 20% to 50% of patients receiving phenytoin long-term. Rare but serious idiosyncratic reactions include hepatitis, bone marrow depression, Stevens-Johnson syndrome, lymphadenopathy, and connective tissue disorders.

Carbamazepine

Pharmacokinetics. Carbamazepine induces its own metabolism, and its clearance can double or triple within the first 12 weeks of therapy.

Therefore, the starting dose should be low, the dosage should be gradually increased, and dosing should be frequent (three or four times daily). The principal metabolite is a 10,11 epoxide that has both anticonvulsant and toxic effects.

Interactions. When valproate is given with carbamazepine, the epoxide metabolite accumulates, producing neurotoxic effects, even if carbamazepine's plasma concentration is in the normal range. Carbamazepine increases the hepatic clearance and decreases the effectiveness of oral anticoagulants, theophylline, haloperidol, and oral contraceptives.

Adverse effects. Transient leukopenia occurs in 10% of patients. Carbamazepine has an antidiuretic hormone-like effect that may be troublesome in elderly cardiac patients. Less common but more serious idiosyncratic side effects are Stevens-Johnson syndrome, exfoliative dermatitis, erythema multiforme, agranulocytosis, and aplastic anemia. Less serious dose-related side effects include drowsiness, dizziness, diplopia, ataxia, nausea, and vomiting.

Valproate

Pharmacokinetics. Valproate is highly protein-bound, but its binding is concentration-dependent and nonlinear. The free fraction increases (as do side effects) at plasma concentrations greater than 75 µg/mL because the protein binding sites are saturated. The free fraction is also higher in elderly patients, because they have reduced hepatic clearance and lower albumin concentrations. The half-life of valproate is 10 hours but is reduced in patients taking multiple antiepileptic drugs.

Interactions. Valproate increases the concentration of carbamazepine epoxide by blocking epoxide hydrolase, and also significantly decreases lamotrigine clearance.

Adverse effects include gastrointestinal distress, tremor, weight gain, alopecia, pancreatitis, and fatal hepatotoxicity.

Phenobarbital

Phenobarbital is the oldest anticonvulsant commonly used and is safe, effective, and inexpensive. However, it is a second-choice medication, owing to its sedative, cognitive, and behavioral side effects.

Interactions. Phenobarbital induces hepatic enzymes and decreases the effectiveness of oral anticoagulants, oral contraceptives, theophylline, antibiotics (doxycycline, griseofulvin), lipophilic beta-blockers, tricyclic antidepressants, and phenothiazines.

Primidone

Pharmacokinetics. Primidone is metabolized to phenobarbital and phenylethylmalonamide, and all three molecules have independent anticonvulsant activity. Approximately 25.1% of the primidone dose is converted to phenobarbital. This allows for anticonvulsant activity at lower levels of phenobarbital.

Interactions. Phenytoin and carbamazepine induce the conversion of primidone to phenobarbital to such an extent that one might as well prescribe phenobarbital. On the other hand, valproate, acetazolamide, and isoniazid inhibit the conversion of primidone to phenobarbital.

Adverse effects. Primidone's long-term side effects are similar to those of phenobarbital.

Ethosuximide

Ethosuximide is the drug of choice for absence seizures. It is not effective in the treatment of generalized tonic-clonic seizures that may accompany absence seizures, and valproate is preferred in such cases. Ethosuximide acts by reducing the low threshold calcium currents in thalamic neurons.

Pharmacokinetics. Ethosuximide is well absorbed orally, and the peak plasma concentration occurs in 1 to 4 hours. It has negligible plasma protein binding, has a half-life of 36 hours, and is eliminated primarily by hepatic metabolism; 10% to 20% of a dose is excreted unchanged in the urine.

Interactions. Ethosuximide does not significantly alter the plasma concentration of other antiepileptic drugs.

Adverse effects include nausea, vomiting, drowsiness, dizziness, ataxia, and psychosis.

NEWER ANTIEPILEPTIC DRUGS

Fosphenytoin

Fosphenytoin is a water-soluble prodrug with a pH of 8.6 to 9. In comparison, intravenous

Check for possible drug interactions with antiepileptic drugs

phenytoin has a pH of 12 in a vehicle of propylene glycol and ethanol. Fosphenytoin is metabolized completely and rapidly to phenytoin in approximately 15 minutes and can be infused 3 times more rapidly than intravenous phenytoin with the same pharmacological effects. It is significantly better tolerated at the infusion site and is recommended for acute treatment of status epilepticus.

Gabapentin

Gabapentin is an analog of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. However, although gabapentin crosses the blood-brain barrier, it does not bind to the GABA receptor. It is FDA-approved for use in adults as an add-on therapy for partial and secondary generalized seizures.

Pharmacokinetics. Gabapentin's absorption is dose-dependent, not dose-proportional—the fraction absorbed decreases as higher doses are given.¹⁵ It has an almost ideal pharmacokinetic profile for an antiepileptic drug: it is not metabolized, does not bind to plasma proteins, and does not appear to possess enzyme-inducing or inhibiting properties. Eighty percent is excreted in the urine and 20% in the feces.

Interactions. Gabapentin does not interact significantly with other antiepileptic drugs or with oral contraceptives.

Adverse effects. Somnolence, dizziness, and ataxia are the most common side effects.

Dosage. The initial dose in adults is 900 mg/day in three divided doses. Doses of 3,600 mg/day have been well tolerated in adults.

Lamotrigine

Lamotrigine appears to be effective in partial and generalized seizures.^{16,17} Reports have also described its efficacy in Lennox-Gastaut syndrome.

Pharmacokinetics. Lamotrigine has linear kinetics, is relatively nonsedating, and does not alter the kinetics of other drugs. It is approximately 55% bound to plasma proteins and has a half-life of 24 to 36 hours.

Interactions. Lamotrigine is eliminated more rapidly in patients taking hepatic enzyme-inducing antiepileptic drugs. In contrast, valproic acid inhibits its metabolism and increases its half-life to 72 hours.

Adverse effects. Dizziness, diplopia, ataxia, and somnolence are the most common adverse effects. Skin rash occurs in about 5% of adult patients; rarely the rash may be severe.

Dosage. For patients taking hepatic enzyme-inducing antiepileptic drugs, treatment with lamotrigine is started at a dose of 50 mg once daily for 2 weeks. The dose can then be increased to 50 mg twice a day for 2 more weeks, followed by increments of 100 mg/day every week, up to a maintenance dose of 300 to 500 mg/day in two divided doses. For patients also taking valproate, the starting dose of lamotrigine should be 25 mg every other day for 2 weeks, then 25 mg/day for the next 2 weeks. Thereafter the dose can be increased by 25 to 50 mg every 1 to 2 weeks up to a maintenance dose of 100 to 150 mg per day on a twice-daily schedule.

Topiramate

Topiramate is indicated for refractory partial and secondary generalized seizures. In several multicenter, double-blind, placebo-controlled trials in the United States, adding topiramate to the regimen reduced the number of seizures by at least 50% in up to 50% of patients with refractory seizures.¹⁸

Pharmacokinetics. Topiramate is rapidly absorbed, has linear pharmacokinetics, is not significantly metabolized, and is predominantly excreted by the kidneys. Protein binding is low, and there are no known differences in effects according to gender, race, or age.

Adverse effects. The most common adverse effects are psychomotor slowing, concentration difficulty, speech and language problems, somnolence, dizziness, and ataxia. Renal stones occur in 1.5% of patients, and paresthesia occurs occasionally.

Vigabatrin

Vigabatrin irreversibly binds to GABA transaminase (the enzyme that breaks down GABA), thereby increasing brain concentrations of GABA. It has demonstrated effectiveness against partial and secondarily generalized seizures and infantile spasms.

Pharmacokinetics. Although vigabatrin's plasma half-life is only 5 to 7 hours, this is

Obtain lab work at baseline and 6–8 weeks after starting therapy



clinically irrelevant in view of its mechanism of action. Excretion is primarily renal.

Adverse effects. The main adverse effects reported in add-on trials were somnolence, fatigue, irritability, depression, and psychosis.

Dosage. In adults, start at 500 mg twice daily and increase by 500-mg increments every week according to the patient's clinical progress, to a total daily dose of 2 to 4 g.

Tiagabine

Tiagabine increases brain levels of GABA by blocking GABA reuptake. It may be effective in intractable complex partial seizures.¹⁹


Pharmacokinetics. Tiagabine is 95% bound to plasma proteins, has a short half-life of 7 hours, and is metabolized in the liver.

Adverse effects include ataxia, dizziness, tremor, and cognitive changes.

Dosage. Doses have ranged from 8 to 56 mg/day, and preliminary reports suggest a dose-dependent effect, with 25% of patients achieving a 50% reduction in seizure frequency.

■ EPILEPSY SURGERY

Surgery is considered for patients whose seizures are refractory despite optimal medical therapy with standard and newer antiepileptic agents for an appropriate time. Careful patient selection is crucial for successful surgery. Before surgery is contemplated, the diagnosis of epilepsy must be ascertained, the epileptic syndrome must be defined and the epileptogenic focus must be precisely localized and resectable without causing significant functional impairment that is worse than the intractable seizures.²⁰

The most common and effective type of focal excisional surgery is temporal lobectomy. Frontal and other extratemporal resections are most effective with structural lesions. The outcome is less favorable with nonlesional extratemporal resections. Corpus callosotomy is a palliative surgery for intractable atonic and secondarily generalized tonic clonic seizures. Functional hemispherectomy is beneficial in patients with seizures arising from a hemisphere with severe contralateral hemiparesis and visual impairment, as in Sturge-Weber syndrome and hemimeganencephaly. 

■ REFERENCES

1. **Commission on Classification and Terminology of the International League Against Epilepsy.** Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981; 22:489-491.
2. **Juul-Jensen P, Foldspang A.** Natural history of epileptic seizures. *Epilepsia* 1983; 24:297-312.
3. **Commission on Classification and Terminology of the International League Against Epilepsy.** Proposal for classification of epilepsies and epileptic syndromes. *Epilepsia* 1985; 26:268-278.
4. **Daly DD.** Ictal clinical manifestations of complex partial seizures. *Adv Neurol* 11:57-83.
5. **King DW, Ajmone-Marsan C.** Clinical features and ictal patterns in epileptic patients with EEG temporal lobe foci. *Ann Neurol* 1977; 2:138-147.
6. **Lindhout D, Schmidt D.** In utero exposure to valproate and neural tube defects (letter). *Lancet* 1986; 2:1392-1393.
7. **Rosa FW.** Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991; 324:674-677.
8. **Berg AT, Shinnar S, Hauser WA, Leventhal JM.** Predictors of recurrent febrile convulsions: a meta-analytic review. *J Pediatrics* 1990; 116:329-337.
9. **Hauser WA.** The natural history of febrile seizures. In: Nelson KB, Ellenberg JH, editors. *Febrile convulsions*. New York: Raven Press, 1980:5-17.
10. **Morton LD, Rizkallah E, Pellock JM.** New drug therapy for acute seizure management. *Semin Pediatr Neurol* 1997; 4:51-63.
11. **Weiss GH, Salazar AM, Vance SC, Grafman JH, Jabbari B.** Predicting posttraumatic epilepsy in penetrating head injury. *Arch Neurol* 1986; 43:771-773.
12. **Weiss GH, Feeney DM, Caveness WF, et al.** Prognostic factors for the occurrence of posttraumatic epilepsy. *Arch Neurol* 1983; 40:7-10.
13. **Treiman DM.** The role of benzodiazepines in the management of status epilepticus. *Neurology* 1990; 40(Suppl 2):32-42.
14. **Hauser WA, Rich SS, Annegers JF, Anderson VE.** Seizure recurrence after a first unprovoked seizure: an extended follow-up. *Neurology* 1990; 40:1163-1170.
15. **Vollmer KO, Archut H, Thomann P, Wagner F, Jahnchen D.** Pharmacokinetic model and absolute bioavailability of the new anticonvulsant gabapentin. *Advances in Epileptology*, vol. 17. New York: Raven Press, 1989:209-211.
16. **Brodie MJ, Richens A, Yuen AWC, for the UK Lamotrigine/Carbamazepine Monotherapy Trial Group.** Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. *Lancet* 1995; 345:476-479.
17. **Steiner TJ, Yuen AWC.** Comparison of lamotrigine and phenytoin in newly diagnosed epilepsy (abstract). *Epilepsia* 1994; 35(Suppl 8):31.
18. **Avanguiz C, McJilton J, Vega M, Ramsay RE.** Safety and effectiveness of three oral doses of topiramate in the treatment of patients with refractory partial epilepsy (abstract). *Epilepsia* 1991; 32(Suppl 3):11.
19. **Chadwick D, Richens A, Duncan J, et al.** Tiagabine HCl: safety and efficacy as adjunctive treatment for complex partial seizures (abstract). *Epilepsia* 1991; 32(Suppl 3):20.
20. **Engel J Jr.** Surgery for seizures. *N Engl J Med* 1996; 334:647-652.

ADDRESS: Harold Morris, MD, Department of Neurology, S-51, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

In 75% of patients, one drug can control seizures