

# Seizure Disorders

Steven C. Schachter, MD<sup>a,b,\*</sup>

## KEYWORDS

- Epilepsy • Seizure • Convulsion
- Diagnosis • Antiepileptic drug

Epilepsy is one of the most common neurologic disorders encountered in clinical practice, affecting an estimated 2 to 4 million people in the United States or approximately 1 in 50 children and 1 in 100 adults.<sup>1</sup> Approximately 1 million women of childbearing age in the United States have epilepsy,<sup>2,3</sup> and the incidence increases over the age of 70 years to more than 100 cases per 100,000 persons.<sup>4</sup>

Despite advances in the sensitivity of diagnostic tests, especially neuroimaging studies, less than half of patients with epilepsy have an identifiable etiology such as congenital brain malformations, inborn errors of metabolism, brain trauma, brain tumors, stroke, intracranial infection, vascular malformations, or cerebral degeneration.<sup>5</sup> In elderly patients, cerebrovascular disease, cerebral degeneration, and brain tumors are more common etiologies than in younger patients.<sup>6</sup>

In as much as epilepsy is characterized by recurrent seizures, the goal of treatment is to completely suppress seizures without causing troublesome side effects or serious idiosyncratic reactions. Antiepileptic drugs (AEDs) are the mainstay of therapy. Because patients with epilepsy also face psychosocial problems such as driving limitations, anxiety or depression, social stigma, and difficulty securing or retaining employment, primary care providers (PCPs) may need to refer patients to other specialists as necessary.

This article reviews the clinical evaluation of epilepsy, pharmacologic treatment, the role of the PCP, and considerations needed for women of childbearing potential and the elderly.

## EVALUATION OF PATIENTS WITH NEW ONSET SEIZURES

The objective of the initial evaluation of a patient with suspected seizures is to exclude other conditions that mimic seizures (**Box 1**) and to look for an underlying cause. The first consideration in selecting an AED is an assessment of the patient's seizure type,

---

Dr. Schachter served as editor-in-chief of [www.epilepsy.com](http://www.epilepsy.com) until October 1, 2008.

<sup>a</sup> Department of Neurology, Harvard Medical School, MA, USA

<sup>b</sup> Department of Neurology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Room K-478, Boston, MA 02215, USA

\* Corresponding author. Department of Neurology, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Room K-478, Boston, MA 02215.

*E-mail address:* [sschacht@bidmc.harvard.edu](mailto:sschacht@bidmc.harvard.edu)

Med Clin N Am 93 (2009) 343–351

doi:10.1016/j.mcna.2008.10.001

0025-7125/08/\$ – see front matter © 2009 Elsevier Inc. All rights reserved.

[medical.theclinics.com](http://medical.theclinics.com)

**Box 1**  
**Differential diagnosis of seizures**

*Neurologic conditions*

- Dementia ("sun downing")
- Migraine (classic, basilar, confusional)
- Movement disorders (tics, Tourette's syndrome, shuddering)
- Periodic paralysis
- Sleep disorders (parasomnias, sleep attacks)
- Syncope
- Transient global amnesia
- Transient ischemic attack

*Psychiatric conditions*

- Conversion disorders
- Disassociation
- Fugue state
- Panic attacks
- Somatization

*Other disorders*

- Breath holding spells
- Cardiac arrhythmia
- Drug intoxication

which, in turn, is based on a seizure description obtained from the patient or witnesses to the seizure. Because the patient may have been unconscious during the seizure, an accurate description of the seizure may only be available from onlookers. Establishing the seizure type also has implications for the likelihood of a cerebral lesion underlying the seizure disorder.

### ***Seizure Types***

The seizure type is usually established from a description of the behaviors that occurred before and during the seizure, as well as after the seizure (the postictal period). The two main seizure types are generalized and partial seizures. Generalized seizures affect both sides of the brain simultaneously and are usually not associated with cerebral pathology. Absence seizures and generalized tonic-clonic seizures (described later) are subtypes of generalized seizures. By comparison, partial seizures arise from a localized area of the cerebral cortex and indicate the possibility of an underlying lesion affecting cortical function.

Symptoms that patients experience when the seizure begins are called simple partial seizures, with "simple" meaning that consciousness is not impaired. Patients may refer to these symptoms as auras or warnings. Typical simple partial seizures include nausea, fear, jerking of one side of the body, or a metallic taste, although a wide variety of auras have been described.<sup>7</sup>

Patients who do not have a conscious warning at the start of their seizures abruptly lose consciousness, which they later may describe as a fadeout or blackout. Three seizure types are characterized by loss of consciousness: complex partial seizures (with “complex” meaning that consciousness is impaired), absence seizures, and generalized tonic-clonic seizures. Because patients are unconscious during these types of seizures, they have no memory of what happened, except perhaps for the warning in complex partial seizures that begin as simple partial seizures.

Complex partial seizures (previously known as temporal lobe seizures and psychomotor seizures) are the most common type of seizure in adults with epilepsy. During complex partial seizures, patients appear awake but do not meaningfully interact with people around them or respond normally to instructions or questions. Instead, patients seem to stare off into space and either remain still or demonstrate repetitive nonpurposeful behaviors (called automatisms), such as chewing, lip smacking, repeating words or phrases, aimless walking or running, or undressing. If patients are forcibly restrained or redirected during complex partial seizures, they may lash out or become aggressive.<sup>8</sup> Complex partial seizures typically last less than 3 minutes and may be immediately preceded by a simple partial seizure, which the patient may or may not remember, and which may occur at times in the same patient without progressing to loss of consciousness. After complex partial seizures, patients may appear confused or somnolent and may complain of a migrainous headache, depressed affect, and embarrassment.

Absence seizures, one of the generalized seizure subtypes, are characterized by the sudden onset of staring with impaired consciousness. They typically last between 5 and 10 seconds and may occur hundreds of times a day, particularly in association with boredom and hyperventilation. They begin in childhood, and 90% of patients have a spontaneous remission before adulthood.

Generalized tonic-clonic seizures (also called grand mal seizures or convulsions), also a subtype of generalized seizures, often begin with a loud scream. The extremities then stiffen (tonic phase), the patient falls to the ground, and cyanosis ensues. After 60 to 90 seconds, the extremities start to jerk, eventually in unison, for an additional 1 to 2 minutes (clonic phase). Bloody frothy sputum may be seen coming out of the patient’s mouth. The termination of the clonic phase represents the onset of the postictal period. The patient appears to be in a deep sleep and then wakes up gradually over minutes to hours, often complaining of a migrainous headache and possibly pain if an injury occurred.

### ***Seizure Triggers***

---

Some patients have seizures in the setting of strong emotions or stress, intense exercise, flashing lights, or loud music. These triggers are often experienced immediately before the seizure. Other physiologic states, including fever, the premenstrual period, and sleep deprivation, may lower the seizure threshold in individual patients and are important to identify so that patients can avoid exposure.

### ***Diagnostic Studies***

---

Testing is appropriate, especially for patients presenting with their first seizure, to exclude significant metabolic dysfunction, infection of the central nervous system, and a cerebral lesion. Laboratory studies include assays for glucose, calcium, and magnesium, hematology studies, renal function tests, and toxicology screens. Patients presenting with a fever or stiff neck should also undergo a lumbar puncture once a mass lesion has been excluded by CT or MRI.

Electroencephalograms (EEGs) are helpful to support the diagnosis of epilepsy and provide evidence in support of classifying a patient's seizure type as generalized or partial; however, EEGs are not sensitive, and more than half of patients with epilepsy have normal initial findings. If the first EEG is normal, it should be repeated with the patient sleep deprived, although the test may still be normal in patients with definite epilepsy. A normal EEG cannot exclude epilepsy assuming the patient is not having a seizure while the EEG is being recorded.

### ***Brain Imaging Studies***

A brain imaging study should be performed in nearly all cases of new onset seizures and especially in patients who present with partial seizures.<sup>9</sup> Brain MRI is more sensitive than CT for most lesions that cause partial seizures. In an emergency, a CT scan is useful to rule out a mass lesion, cerebral hemorrhage, or stroke. As is true for EEGs, nearly half of patients with epilepsy have normal or nonspecifically abnormal studies. MRI scans should be repeated over time if there is progressive worsening of the patient's neurologic examination, cognitive function, or seizure frequency or severity.

### **GOALS OF THERAPY AND WHICH ANTIEPILEPTIC DRUGS SHOULD BE PRESCRIBED**

The goal of treatment is to completely suppress seizures without causing intolerable side effects.<sup>10,11</sup> Initial treatment with an AED achieves these goals in as many as 70% of patients. The prognosis for seizure control in the other 30% is less favorable. These patients may require numerous trials of AEDs, either as monotherapy or combination therapy.<sup>11</sup>

Nearly 20 drugs are available in the United States for the treatment of epilepsy. Pharmacologic characteristics differ significantly from one AED to another (**Table 1**). For example, some AEDs are nearly completely protein bound in the serum (eg, phenytoin and valproate), whereas others are not protein bound at all (gabapentin and levetiracetam). The plasma half-life of AEDs ranges from 12 hours to 4 days, and a steady state is reached after 3 days to 3 weeks depending on the specific AED. Most AEDs are metabolized by the liver and excreted by the kidney; therefore, compromised hepatic function decreases the metabolism of certain AEDs, and impaired renal function reduces the rate of drug clearance of renally excreted AEDs.

The primary side effects associated with AED therapy (**Table 2**) are referable to the central nervous system and include headache, dizziness, drowsiness, ataxia, double vision, slurred speech, and confusion. The severity of these side effects usually parallels the titration rate, the total daily dose, and the number of concomitantly prescribed AEDs (polytherapy). Mild side effects tend to diminish or resolve over time or with dosage adjustment, but more pronounced symptoms may persist and interfere with the patient's cognitive or behavioral functioning. Other common side effects include rash, nausea, vomiting, and weight gain or loss. Idiosyncratic reactions such as symptomatic hyponatremia, pancreatitis, agranulocytosis, hepatic dysfunction or failure, serum sickness, and Stevens-Johnson syndrome are rare but may be serious and even fatal. Screening laboratory studies, including blood counts, and liver and renal function tests should generally be obtained before initiation of treatment to provide a baseline and repeated if clinically indicated.<sup>12</sup>

Selection of AEDs should be based on their Food and Drug Administration (FDA) indication, the patient's seizure type, the pharmacokinetic profile of the drug, the potential for adverse effects and drug-drug interactions, and cost. With the exception of medical emergencies, therapy should be initiated with a low dose and increased

**Table 1**  
**Pharmacokinetic profiles of selected AEDs**

Drug	Plasma Protein Binding (%)	$t_{1/2}$ (h) <sup>a</sup>	Time to Steady-State Serum Level (Days)	Therapeutic Serum Level ( $\mu\text{g/mL}$ )
Carbamazepine	70–80	11–17	3–10	4–12
Ethosuximide	0	40–50	6–12	40–100
Gabapentin	0	5–7	1–2	Not established
Lamotrigine	50–55	10–15	5–15	Not established
Levetiracetam	<10	7–8	2–3	Not established
Oxcarbazepine	40	8–10	3–4	Not established
Phenytoin	90	15–30	5–15	10–20
Pregabalin	0	6	2–3	Not established
Topiramate	9–17	20–24	5	Not established
Valproate	60–95	6–18	2–4	50–150

<sup>a</sup>  $t_{1/2}$  = half-life.

slowly until seizures are completely controlled or until bothersome side effects occur that persist. **Table 3** lists the AEDs suggested by a recent survey of epilepsy specialists as first-line therapy. This list differs in some respects from FDA indications; therefore, a comparison with the FDA indications found in package inserts is warranted.<sup>13</sup> If the initial AED fails to control seizures or produces intolerable side effects before an adequate serum concentration is reached, another AED should be tried. The dosage of the first AED should be tapered as the dosage of the substitute AED is titrated upward to a therapeutic level.

Dosing schedules can be found in package inserts and usually are a function of the half-life of the AED.<sup>14</sup> Drugs with long half-lives, such as phenobarbital or extended-release preparations, can be taken once or twice daily, whereas those with relatively short half-lives, such as immediate release carbamazepine, may need to be taken three to four times a day.

#### KEYS TO MAINTAINING PATIENT COMPLIANCE

Patient compliance with the dosing schedule is crucial to maintaining seizure control without side effects. Noncompliance may result in an increase in seizure frequency or severity, side effects, or higher or lower than usual AED serum concentrations. Noncompliance usually is an indication of a communication barrier in which the importance of regularly taking the medication is not understood by the patient, but other causes include memory lapses, complicated AED regimens, denial of illness, and fixed incomes. Patient education, the use of pill boxes, and engaging members of the patient's support system may be helpful.

#### THE ROLE OF THE PRIMARY CARE PROVIDER

In many instances, PCPs make the diagnosis of epilepsy, initiate therapy, and schedule regular follow-up visits to assess seizure frequency, side effects, and compliance. PCPs may also refer patients to a neurologist for further diagnostic and therapeutic suggestions, particularly if the diagnosis is in question, if the seizures do not respond to initial therapy, or to assess the feasibility of discontinuing AEDs. For patients whose

**Table 2**  
Adverse effects of selected AEDs

Drug	Systemic Effects	Neurotoxic Effects	Rare Idiosyncratic Reactions
Carbamazepine	Nausea, vomiting, diarrhea, hyponatremia, rash, pruritus, fluid retention	Drowsiness, dizziness, blurred or double vision, lethargy, headache	Agranulocytosis, Stevens-Johnson syndrome, <sup>a</sup> toxic epidermal necrolysis, <sup>a</sup> aplastic anemia, hepatic failure, dermatitis/rash, serum sickness, pancreatitis
Ethosuximide	Nausea, vomiting	Sleep disturbance, drowsiness, hyperactivity	Agranulocytosis, Stevens-Johnson syndrome, hepatic failure, dermatitis/rash, serum sickness
Gabapentin	Fluid retention	Somnolence, dizziness, ataxia	Unknown
Lamotrigine	Rash, nausea	Dizziness, somnolence	Stevens-Johnson syndrome, hypersensitivity syndrome
Levetiracetam	Unknown	Somnolence, dizziness, headache, anorexia, nervousness, irritability	Unknown
Oxcarbazepine	Rash, hyponatremia	Drowsiness, dizziness, headache, diplopia, nausea, vomiting, ataxia	Unknown
Phenytoin	Gingival hypertrophy, body hair increase, rash, lymphadenopathy	Confusion, slurred speech, double vision, ataxia, neuropathy (with chronic use)	Agranulocytosis, Stevens-Johnson syndrome, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness
Pregabalin	Fluid retention	Somnolence, dizziness, asthenia, ataxia, headache	Unknown
Topiramate	Anorexia	Ataxia, poor concentration, confusion, dizziness, fatigue, paresthesia, somnolence, word-finding difficulty, cognitive slowing, depression	Nephrolithiasis, glaucoma, metabolic acidosis
Valproate	Weight gain, nausea, vomiting, hair loss, easy bruising	Tremor	Agranulocytosis, Stevens-Johnson syndrome, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness, pancreatitis

<sup>a</sup> Stevens-Johnson syndrome and toxic epidermal necrolysis are significantly more common in patients with the human leukocyte antigen (HLA) allele, HLA-B\*1502, which occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Patients with ancestry from areas in which HLA-B\*1502 is present should be screened for the allele before starting treatment with carbamazepine. If these individuals test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions.

**Table 3**  
**Recommended AEDs for adults according to seizure type<sup>13</sup>**

Seizure Type	First-Line Therapy (In Alphabetical Order)
Primary generalized tonic-clonic seizures	Valproate, lamotrigine, topiramate
Partial seizures	—
Adult	Carbamazepine, lamotrigine, oxcarbazepine
Elderly	Lamotrigine, levetiracetam
Absence seizures	Valproate, ethosuximide, lamotrigine

seizures do not respond to initial therapy, other AEDs are typically suggested by the neurologist, either alone or in combination with the initial AED. Patients with seizures that are resistant to multiple trials of AEDs may be candidates for nonpharmacologic treatments, including diet-based approaches (ketogenic diet, low glycemic index diet, modified Atkins diet), brain surgery, or vagus nerve stimulation. Patients with epilepsy usually require chronic therapy and follow-up, which is often provided by the PCP.

The care that patients with epilepsy require often goes beyond AEDs because they may have psychosocial problems, cognitive impairments, affective disorders (most commonly depression or anxiety),<sup>8</sup> and educational or vocational needs. The PCP should work in close cooperation with other medical and social services professionals, as well as involve family members as necessary.

#### ADVICE FOR PATIENTS

First and foremost, the PCP should discuss the diagnosis and the proposed treatment plan, and he or she should go over these details on subsequent visits until the patient clearly understands and is an active partner in the treatment process, particularly with regard to compliance with AED treatment and lifestyle modifications.

Patients should be advised to eat a healthy diet, to obtain regular and sufficient sleep to avoid daytime drowsiness, to avoid illicit drugs and alcohol (other than an occasional glass of beer or wine), and to alert the PCP if there are any changes in their concomitant medications, including over-the-counter drugs, herbs, and vitamin supplements. Patients and those around them should learn how to respond to a seizure and the circumstances that should prompt emergency attention (eg, repeated seizures or injury). Patients whose seizures are caused by specific situations, such as flashing lights or loud music, should plan ahead to minimize their exposure to these forms of stimulation. Helpful Web sites for patients include [www.epilepsyfoundation.org](http://www.epilepsyfoundation.org) and [www.epilepsy.com](http://www.epilepsy.com).

#### CONSIDERATIONS APPLYING TO WOMEN OF CHILDBEARING AGE AND THE ELDERLY

##### *Women of Childbearing Age*

Nearly 1 million women of childbearing potential in the United States have epilepsy.<sup>2,15</sup> The issues uniquely faced by women pertain to fertility, contraception, and pregnancy. Fertility may be reduced by the neuroendocrine effects of some AEDs or as a consequence of epilepsy.<sup>16</sup> Likewise, hepatic enzyme-inducing AEDs may lower the potency of hormonal contraceptives, resulting in contraceptive failure.<sup>2</sup>

All AEDs are potentially teratogenic. Data to indicate which AED is associated with the lowest likelihood of birth defects are not currently available. The overall risk of birth defects in the offspring of epileptic women who take AEDs is 5% to 6%, or

approximately twice the rate in the general population.<sup>12</sup> The most frequently seen birth defects are neural tube defects (especially in association with valproate and carbamazepine), cleft lip, cleft palate, heart defects, and microcephaly. Therapy with two or more AEDs concomitantly significantly increases the risk of malformations. Preconception treatment with 0.4 to 4 mg/day of folic acid may reduce the risk of fetal malformations in women who become pregnant, although research to support this recommendation is lacking. High resolution level II fetal ultrasonography should be performed at 16 to 18 weeks of gestation to detect neural tube defects, cardiac anomalies, and limb defects.<sup>2</sup> Amniocentesis and serum alpha-fetoprotein levels may also be useful.<sup>2,12</sup>

Seizure frequency increases during pregnancy in approximately one of three patients because of hormonal and metabolic changes, sleep deprivation, stress, and noncompliance (mainly because women may discontinue AEDs out of fear of birth defects).<sup>2</sup> AED serum levels may decline steadily during pregnancy because of physiologic changes that affect AED pharmacokinetics, often requiring dosage increases. Serum levels of these AEDs usually rise postpartum.

### ***Elderly Patients***

In older adults, the prevalence of epilepsy steadily increases with age. Within a few decades, it is predicted that nearly half of patients with new onset epilepsy will be aged more than 65 years. Contributing factors are Alzheimer's disease, cerebrovascular disease, brain tumor, head injuries, and alcohol or drug abuse.<sup>17</sup> Seizures in the elderly may be mistaken for dementia, cerebrovascular insufficiency, or cardiac problems.

The pharmacology of AEDs is different in elderly patients than in young adults because of age-related changes in absorption, distribution, water-to-fat ratio, and liver and renal function.<sup>11</sup> In addition, protein binding is lower in elderly patients. The risk of drug-drug interactions is higher in this age group because concomitant drugs are often taken for comorbid medical conditions. The result of these factors is a higher propensity for AED-related side effects. This possibility can be minimized by initiating AED therapy with a lower dose and titrating more slowly than in young adults, aiming for a lower target serum concentration than in younger patients.<sup>11</sup>

### **SUMMARY**

The goal of epilepsy treatment is to eliminate seizures without significant side effects. The large majority of patients achieve these goals. The PCP has a central role in the diagnosis and treatment of epilepsy and may work collaboratively with neurologists and other health care professionals according to the needs of individual patients.

### **REFERENCES**

1. Hauser WA, Hesdorffer DC. *Epilepsy: frequency, causes and consequences*. New York: Demos; 1990.
2. Devinsky O, Yerby MS. Women with epilepsy: reproduction and effects of pregnancy on epilepsy. *Neurol Clin* 1994;12:479-95.
3. Morrell MJ. Guidelines for the care of women with epilepsy. *Neurology* 1998; 51(5 Suppl 4):S21-7.
4. Loiseau J, Loiseau P, Duche B, et al. A survey of epileptic disorders in southwest France: seizures in elderly patients. *Ann Neurol* 1990;27:232-7.
5. Schachter SC. Iatrogenic seizures. *Neurol Clin* 1998;16:157-70.
6. Azar NH, Abou-Khalil BW. Epilepsy in the elderly. *Semin Neurol* 2008;28(3): 305-16.

7. Schachter SC, editor. *Epilepsy in our words: personal accounts of living with seizures*. Oxford (UK): Oxford University Press; 2008.
8. Marcangelo MJ, Ovsiew F. Psychiatric aspects of epilepsy. *Psychiatr Clin North Am* 2007;30(4):781–802.
9. Cascino GD. Neuroimaging in epilepsy: diagnostic strategies in partial epilepsy. *Semin Neurol* 2008;28(4):523–32.
10. Pellock JM, Willmore LJ. A rational guide to routine blood monitoring in patients receiving antiepileptic drugs. *Neurology* 1991;41:961–4.
11. Elger CE, Schmidt D. Modern management of epilepsy: a practical approach. *Epilepsy Behav* 2008;12(4):501–39.
12. So EL. Update on epilepsy. *Med Clin North Am* 1993;77(1):203–14.
13. Karceski S, Morrell M, Carpenter D. The treatment of epilepsy in adults: expert opinion, 2005. *Epilepsy Behav* 2005;7(Suppl 1):1–64.
14. Wyler AR. Modern management of epilepsy: recommended medical and surgical options. *Postgrad Med* 1993;94(3):97–8 [103–8].
15. Herzog AG, Schachter SC. Valproate and the polycystic ovarian syndrome: final thoughts. *Epilepsia* 2001;42(3):311–5.
16. Hamed SA. Neuroendocrine hormonal conditions in epilepsy: relationship to reproductive and sexual functions. *Neurologist* 2008;14(3):157–69.
17. Hauser WA. Seizure disorders: the changes with age. *Epilepsia* 1992;33(Suppl 4):S6–14.