Seizures and Epilepsy: An Approach to Diagnosis and Management

Case Study and Commentary, Myrka R. Torres, MD, Geoffrey L. Ahern, MD, PhD, and David M. Labiner, MD

Epilepsy is a chronic brain disorder characterized by recurrent seizures. A seizure is an abnormal discharge of cortical neurons that can result in a variety of clinical manifestations. Epilepsy affects more than 2.5 million individuals in the United States, or approximately 1% of the population. It has been estimated that nearly 10% of the population will have a seizure at some point in their lifetime [1]. The economic impact of epilepsy is considerable, reaching $12.5 billion in direct and indirect costs [2].

Many patients with a single seizure or with recurrent seizures (epilepsy) can be safely and appropriately managed in the primary care setting. In this article, we present a case that illustrates key diagnostic and therapeutic considerations in the management of an individual with seizures.

CASE STUDY

Initial Presentation

A 28-year-old left-handed woman is seen urgently by her primary care physician because of a reported first-time seizure.

History

The seizure occurred 5 days prior to the visit. The patient was in a meeting at work when she experienced a sense of impending doom accompanied by an alteration in her hearing—“things sounded far-off.” She was amnesic for events following the seizure, which included witness-reported generalized stiffening of her body followed by rhythmic jerking. She fell and lost control of her bladder. On further questioning, the patient reports a history of panic attacks. She characterizes these as a feeling of doom associated with the sense that sounds are far-off, much the way she described the feelings that preceded her seizure. These “panic attacks” have occurred randomly throughout the past 2 years and are stereotypic. She has never received treatment for these spells. She takes no medications except for over-the-counter multivitamins.

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The patient is the product of a full-term, uncomplicated pregnancy with normal labor and delivery and had early childhood development. There is no history of febrile seizures, meningitis, encephalitis, or significant head trauma nor a family history of seizures or epilepsy. The patient’s past medical history is unremarkable except for an allergy to sulfa medications. The family history is noncontributory. She is an executive and is married with 2 young children. She reports occasional alcohol consumption but denies the use of tobacco or illicit drugs. She denies any HIV risk factors. Her review of systems is notable only for her being mildly nearsighted. Her obstetrical history is gravida 2, para 2. Her menstrual periods are regular.

Physical Examination

The patient appears well developed and well nourished. Blood pressure is 100/70 mm Hg, pulse is 80 bpm, and temperature is 98.2°F. She is alert and fully oriented. Mental status is normal. Examination of the cranial nerves is normal as is the motor and sensory examination. Reflexes are intact and symmetric throughout. Her gait is normal. Her general physical examination is likewise normal.

What tests are used to evaluate the patient with a first seizure?

The evaluation of a first seizure may include a complete blood count (CBC), electrolytes, liver function tests, thyroid function tests, blood alcohol level, urinalysis, and a toxicology screen. Not all tests are necessary for every patient, and the evaluation should be tailored to the clinical situation. The timing of the seizure relative to the evaluation will help determine which of the studies is appropriate. Additionally, neuroimaging should be performed. Often a computed tomography (CT) scan is obtained in the emergency setting, although the best imaging modality in the evaluation of seizures is magnetic resonance imaging (MRI). In certain circumstances, it may be appropriate to defer emergency imaging and wait to obtain the MRI, such as when the patient has fully recovered from the seizure and the initial emergency evaluation is normal. The MRI assessment should include coronal views (T1, T2, and FLAIR) to better visualize the temporal lobes and hippocampi. At times, performing the MRI with gadolinium enhancement may be appropriate.

Finally, the electroencephalogram (EEG) is an important part of the initial (but not emergent) part of the evaluation. An EEG may show abnormalities that facilitate classification of the type of seizure and help determine if therapy is appropriate. Obtaining an EEG with the patient both awake and asleep, as well as with activation procedures such as hyperventilation and photic stimulation, can maximize the yield of the study. It is important to remember that an EEG can be completely normal in an individual with epilepsy.

Initial Test Results

The patient’s initial emergency department evaluation included laboratory studies that revealed a normal CBC and electrolytes, except for a phosphorous level of 1.5 mg/dL (normal, 2.5–4.5 mg/dL). A CT scan showed no intracranial abnormalities. An EEG performed 4 days after the event revealed a normal background both awake and asleep. Activation procedures produced no abnormalities. Left temporal spikes were observed throughout the study. These were reported to be consistent with partial seizures.

What is the diagnosis in this patient?

The differential diagnosis of seizure can include metabolic abnormalities, acute drug intoxication, alcohol withdrawal, syncope, transient ischemic attack, sleep disorders, panic attacks, and a psychogenic or behavioral abnormality. In this patient, however, the history as well as the initial workup is strongly suggestive of seizure. There is little doubt that the patient had a tonic-clonic seizure (given the witnessed account), but both the history of aura and the focality on the EEG (ie, left temporal spikes) strongly suggest that the correct diagnosis is a partial onset seizure with secondary generalization (Table 1) [3]. In retrospect, the “panic attacks” likely represent simple partial seizures. In light of the patient’s age and focality on the EEG, it would be prudent to perform an MRI scan to exclude such entities as a low-grade tumor, neuronal migrational abnormality, or other lesion that may not be visualized on a CT scan. Such a study does not have to be performed emergently but should be done in a timely fashion.

Diagnosis

The physician seeks a consult with a neurologist. The neurologist informs the patient that she has a diagnosis of partial-onset epilepsy with secondary generalization. They recommend that the patient have an MRI. The patient undergoes an MRI study, which is normal.

What issues should be considered when deciding whether to initiate medical therapy for a first seizure?

Likelihood of Recurrence

Once the initial evaluation is complete and it has been determined that the patient likely had a seizure, the physician,
often in consultation with a neurologist, must decide whether to treat the patient with an anticonvulsant. While this decision should be individualized, the key issue is estimating the patient’s risk of seizure recurrence. The literature is somewhat controversial in answering this question. In 1881, Gowers [4] suggested that “seizures beget seizures,” which if correct would suggest that all patients with seizures should be treated. Until the 1960s, it was generally thought that few people would remit and in fact most would develop chronic epilepsy; therefore, the standard of care was to treat patients with anticonvulsants. Since that time, well-done epidemiologic studies have shown that significant numbers of patients (up to 2 out of 3) will never have a recurrence following a single seizure [5-7]. Recurrent seizures, based on the World Health Organization definition, is the \textit{sine qua non} of epilepsy, and epilepsy should be treated. Recent data suggest that the risk of recurrence following a second or third seizure is considerable [8] and therefore requires intervention.

A seizure is defined as the clinical manifestation of an abnormal electrical discharge of neurons. Risk factors for

<table>
<thead>
<tr>
<th>Types of Seizures</th>
<th>Major Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial seizures</td>
<td>Consciousness and ability to interact with the external environment are not impaired\nMotor signs: tonic (tension) or clonic (contraction and relaxation of muscles in rapid succession) movements of a discrete body part\nOR\nSomatosensory or special sensory symptoms: localized paresthesias, unformed visual imagery, unpleasant olfactory or gustatory sensations, vertigo, sounds, formed visual hallucinations\nOR\nAutonomic symptoms or signs: epigastric rising or distress, nausea, or lightheadedness, pallor, flushing, sweating, piloerection, pupillary dilatation, cardiac arrhythmias, incontinence\nOR\nPsychic symptoms: feelings of \textit{déjà vu} or unfamiliarity (\textit{jamais vu}), forced thinking, cognitive disturbances, depersonalization, time distortion, fear, rage</td>
</tr>
<tr>
<td>Complex partial seizures (formerly known as psychomotor seizures)</td>
<td>Aura followed by impaired consciousness</td>
</tr>
<tr>
<td>Partial seizures with secondary generalization</td>
<td>Aura or complex partial seizure followed by impaired consciousness\nTonic-clonic (convulsive) movements</td>
</tr>
<tr>
<td>Generalized seizures</td>
<td>Lapses of consciousness that usually last no more than 10 seconds accompanied by rapid eye blinking</td>
</tr>
<tr>
<td>Absence seizures (formerly known as petit mal seizures)</td>
<td>Muscle jerks in isolated muscle groups such as facial muscle groups or in the entire body\nConsciousness is not impaired</td>
</tr>
<tr>
<td>Myoclonic seizures</td>
<td>Tonic spasms of truncal and facial muscles with associated flexion or extension of the extremities\nImpaired consciousness</td>
</tr>
<tr>
<td>Tonic seizures</td>
<td>Sudden loss of muscle tone that can be mild, causing a brief head drop, or severe, leading to sudden collapse</td>
</tr>
<tr>
<td>Atonic seizures (drop attacks)</td>
<td>Usually begin before age 3 years\nSimilar to tonic-clonic seizures (without the tonic component)\nMay be asymmetric\nLoss of consciousness; confusion may follow seizures</td>
</tr>
<tr>
<td>Clonic seizures</td>
<td>Similar to secondarily generalized seizures, but they begin without an aura or complex partial seizure\nMay be preceded by headache, insomnia, mood change, or irritability\nLoss of consciousness\nConfusion, lethargy, or paralysis may follow seizure\nTongue biting or urinary incontinence may occur</td>
</tr>
<tr>
<td>Tonic-clonic seizures (formerly known as grand mal seizures or convulsions)</td>
<td>Similar to secondarily generalized seizures, but they begin without an aura or complex partial seizure\nMay be preceded by headache, insomnia, mood change, or irritability\nLoss of consciousness\nConfusion, lethargy, or paralysis may follow seizure\nTongue biting or urinary incontinence may occur</td>
</tr>
</tbody>
</table>


*Known as auras when they precede a complex or secondarily generalized seizure.
The traditional AEDs that were available before 1993 include phenobarbital, primidone, phenytoin, ethosuximide, carbamazepine, and valproate [16]. These AEDs have been studied extensively, and many are still widely used, accounting for over 75% of all AEDs used for treating seizures. The traditional AEDs provide the advantages of broad familiarity, known efficacy, generally low cost, and coverage by insurers [15]. However, many of these agents are associated with either adverse effects or lack of efficacy [17]. Eight new medications have become available in the United States in the past decade. These newer AEDs have comparable efficacy but generally have more favorable side effect profiles than the traditional medications (Table 3). This benefit is tempered by the relative cost of the newer medications [18].

The safety and efficacy of 3 different doses of gabapentin (300 mg/day, 900 mg/day, and 1800 mg/day) were compared with carbamazepine (600 mg/day) in a study that enrolled 275 adolescents and adults with newly diagnosed epilepsy who require treatment can be initiated on standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital or on the newer AEDs such as lamotrigine, gabapentin, oxcarbazepine, or topiramate [15]. The effectiveness of tiagabine, zonisamide, or levetiracetam in newly diagnosed patients cannot be determined with the data that are currently available.

Once the decision to treat has been made, the treating physicians must pick the most appropriate medical therapy. While treatment is often initiated in the emergency setting based on the available parenteral medications, this choice is not irrevocable. Medication should be selected based on the patient’s seizure type and the side effect profile, and cost and compliance factors should also be considered.

A variety of medications are available to achieve the fundamental goal of epilepsy therapy of "no seizures and no side effects." Both the older and newer antiepileptic drugs (AEDs) are generally equally effective in treating new-onset epilepsy [15]. According to recent treatment guidelines developed by the AAN, patients with newly diagnosed epilepsy who require treatment can be initiated on standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital or on the newer AEDs such as lamotrigine, gabapentin, oxcarbazepine, or topiramate [15]. The effectiveness of tiagabine, zonisamide, or levetiracetam in newly diagnosed patients cannot be determined with the data that are currently available.

### Benefits versus Risks of Antiepileptic Drugs

Treatment appears to reduce the risk of recurrent seizures in many but not all treated patients. In one study, 2 of 14 children treated with carbamazepine following a single seizure had recurrent seizures, whereas 9 of 17 without treatment had recurrent seizures [11]. In a second larger study, the risk of recurrence in the absence of treatment was 2.8 times greater than if treatment were administered [12]. Treatment reduced the risk independent of age, seizure etiology, or EEG abnormalities. Although these data may push one toward treating a single seizure, the potential benefits must be carefully weighed against the risks of treatment. Up to 33% of patients on chronic antiepileptic therapy report adverse reactions [13]. Even monotherapy, which is thought to be far better tolerated than polypharmacy, causes problems in 20% of patients [13]. These adverse events often lead to treatment failure. There appears to be a greater susceptibility to adverse effects in the very young and the elderly, although no age-group is immune. Additionally, individuals with other medical problems and those taking other medications may be more vulnerable. Other factors that need to be considered include driving, financial and insurance issues, likelihood of compliance, and social and cultural issues such as employment and education. No matter what decision is made regarding treatment, the patient (or parents) should be counseled regarding risks and benefits of the decision. Special restrictions may be placed on the patient (eg, limitations at work and driving). Ultimately, the decision of whether to treat a first seizure should be individualized as advised in the guidelines of the American Academy of Neurology (AAN) [14].

### How do traditional AEDs compare with newer agents?

The safety and efficacy of 3 different doses of gabapentin (300 mg/day, 900 mg/day, and 1800 mg/day) were compared with carbamazepine (600 mg/day) in a study that enrolled 275 adolescents and adults with newly diagnosed epilepsy...
Essentially any of the traditional or newer AEDs (with the exception of ethosuximide because it is indicated for absence seizures) may be appropriate in treating this patient. Most of the newer generation of medications work in the treatment of partial-onset seizures, although not all are indicated for use in monotherapy. Had this patient had primary generalized onset of seizures, the choices would be more limited. Of the newer generation of medications, either lamotrigine or oxcarbazepine, would be reasonable choices. They are as effective as the traditional AEDs but better tolerated as a group. Lamotrigine is weight-neutral and has mood elevating properties. However, titration is slow (greater than 1 month) to avoid the risk of dermatologic reactions. Levetiracetam is quickly titrated and has no interactions with other medications as well as limited side effects, making it another good choice. However, it is not yet indicated as monotherapy. Topiramate has been associated with cognitive side effects, although these can be avoided if it is titrated slowly. Zonisamide, a sulfa drug, would not be appropriate in this patient due to her allergy; although it might otherwise be a reasonable choice.

**CASE-BASED REVIEW**

- **What issues must be considered when prescribing AEDs in women?**

A discussion of all of the issues to consider when prescribing medications to a woman with epilepsy is beyond the scope of this paper but is thoroughly reviewed elsewhere [21], and guidelines for management of this population have been adopted by the AAN [22]. In a woman of childbearing age, one should consider choosing a medication that is first and foremost effective for the type of seizures she has. A second major consideration is the risk of birth defects. Recent studies demonstrate that some medications are clearly associated with teratogenesis (phenobarbital and valproate), while others may have a lower risk [23–26]. The population risk of having a child with a major malformation is between 2% and 3%. The majority of antiepileptic medications essentially double that risk to 4% to 6%. Valproate has an added 1% to 2% risk of neural tube defects. On the other hand, lamotrigine appears to have no increased risk over the population risk of malformations [24]. Perhaps the most important fact to remember when treating a woman with epilepsy is that any woman on AEDs during pregnancy has a greater than 90% likelihood of having a totally normal pregnancy outcome. With that in mind, Table 4 lists the risk of birth defects

- **What agents can be selected to fit this patient’s needs?**

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**Decision to Treat**

The primary care physician in consultation with the neurologist assesses the patient’s risk of seizure recurrence at greater than 60% due to her history and EEG findings. In light of this high risk, the physician elects to start her on medication. The patient has a sulfa allergy. In addition, she is of childbearing age and has stated that she wants a nonsedating medication so that she can remain focused at work.
associated with different antiseizure medications. When treating a patient like the case patient, the primary consideration should be to use a medication at the lowest effective dose that will control seizures and when possible, to pick a category C medication. Additionally, all women who are of childbearing age should also take folate supplementation (either alone or in a prenatal vitamin). The ideal dose of folate is not clear but ranges from 1 to 4 mg per day for a woman on AEDs. The Centers for Disease Control and Prevention recommends 0.4 mg folate daily for all women.

Issues regarding bone health, while not unique to women, have recently come to light [27]. Some of the older AEDs that are enzyme-inducing drugs (carbamazepine, phenobarbital, and phenytoin) can cause osteopenia or osteoporosis. These potential effects on bone may be a reason to select a noninducing medication for a specific patient or at minimum may be the rationale for obtaining a bone density study.

**Initiation of Therapy**

The physician initiates therapy with lamotrigine with a slow titration to a target dose of 200 mg daily to control her seizures and also prescribes prenatal vitamins with 1 mg folate as the patient has stated that she may want another child. As the initial titration of lamotrigine takes at least 5 weeks, the patient is asked to follow up in 2 months. She is also advised to contact the physician if she develops a skin reaction or other problems.

**Monitoring and Restrictions**

Ongoing monitoring of the patient on medication is appropriate and can be done either by the primary care physician or the neurologist. Patients who receive treatment should be monitored both for compliance and the presence of adverse reactions from therapy. Serum concentrations can be monitored, but it should be remembered that if the individual is free of seizures and side effects, the levels may be less relevant. For instance, a phenytoin level of 9.5 µg/dL (normal therapeutic range, 10–20 µg/dL) should not be considered subtherapeutic if the patient is seizure-free. Serum concentrations can be used (when necessary) to monitor patient compliance. Further blood work, including CBC, liver function tests, and electrolytes, may be monitored periodically in certain patients but may not be needed routinely [28].

In all states, driving restrictions are placed on individuals who have had seizures. It is important that all health care

### Table 3. Antiepileptic Drug Information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Names*</th>
<th>Starting Dose, mg/day</th>
<th>Maintenance Dose, mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Carbatrol</td>
<td>400</td>
<td>600–1200</td>
</tr>
<tr>
<td></td>
<td>Tegretol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tegretol-XR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atretol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epitol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Generic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>Depakote</td>
<td>500–1000</td>
<td>1000–3000</td>
</tr>
<tr>
<td></td>
<td>Depacon</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depakene</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Generic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>Zarontin</td>
<td>500</td>
<td>1000–3000</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Generic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Lamictal</td>
<td>50</td>
<td>300–500</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Neurontin</td>
<td>900</td>
<td>900–3600</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Lamictal</td>
<td>50</td>
<td>300–500</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Keppra</td>
<td>1000</td>
<td>1000–3000</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Trileptal</td>
<td>600</td>
<td>600–2400</td>
</tr>
<tr>
<td>Phenobarbital (also other</td>
<td>Generic</td>
<td>90</td>
<td>90–120</td>
</tr>
<tr>
<td>barbitals)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin (diphenylhydanto-</td>
<td>Dilantin</td>
<td>300</td>
<td>300–500</td>
</tr>
<tr>
<td>ian) (also other hydantoin)</td>
<td>Phenytek</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Generic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>Mysoline</td>
<td>100–125</td>
<td>750–1000</td>
</tr>
<tr>
<td></td>
<td>Mydione</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Generic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Gabitril</td>
<td>4</td>
<td>32–56</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Topamax</td>
<td>25–50</td>
<td>200–400</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Zonegran</td>
<td>100</td>
<td>400–600</td>
</tr>
</tbody>
</table>

Adapted from reference 18.

*Brand and price information from Drugs.com (30 Aug 2004).
†Some of the indications mentioned are not currently approved by the U.S. Food and Drug Administration.
<table>
<thead>
<tr>
<th>Dosing Interval</th>
<th>Therapeutic Range (µg/mL)</th>
<th>Major Toxicsities</th>
<th>Seizure Indications†</th>
<th>Relative Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or 3 times daily</td>
<td>4–12</td>
<td>Skin rash (5%–10%, rarely serious), liver enzyme elevation, transient neutropenia, aplastic anemia (extremely rare), low serum sodium</td>
<td>Generalized tonic-clonic</td>
<td>$</td>
</tr>
<tr>
<td>2 or 3 times daily</td>
<td>50–150</td>
<td>Nausea, weight gain, tremor, hair loss, blood dyscrasias, rare hepatotoxicity, rare edema, menstrual irregularities, spina bifida is a teratogenic effect (1%–2%)</td>
<td>Generalized tonic-clonic Simple and complex partial Absence Myoclonic and atonic Lennox-Gastaut syndrome</td>
<td>$$$</td>
</tr>
<tr>
<td>2 times daily</td>
<td>40–120</td>
<td>Gastrointestinal upset</td>
<td>Absence</td>
<td>$–$$</td>
</tr>
<tr>
<td>3 times daily</td>
<td>4–8</td>
<td>Well tolerated</td>
<td>Simple and complex partial including secondary generalization</td>
<td>$$$</td>
</tr>
<tr>
<td>1 or 2 times daily</td>
<td>2–20</td>
<td>Skin rash (5%–10%, rarely serious), insomnia</td>
<td>Generalized tonic-clonic Simple and complex partial Lennox-Gastaut syndrome Myoclonic</td>
<td>$$$$</td>
</tr>
<tr>
<td>2 times daily</td>
<td>20–60</td>
<td>Somnolence, asthenia, headache</td>
<td>Generalized tonic-clonic Simple and complex partial</td>
<td>$$$</td>
</tr>
<tr>
<td>2 times daily</td>
<td>5–50</td>
<td>Hyponatremia, sleepiness, psychomotor slowing, cross-reacts with carbamazepine</td>
<td>Simple and complex partial Generalized tonic-clonic</td>
<td>$$$</td>
</tr>
<tr>
<td>Once daily</td>
<td>10–45</td>
<td>Sedation</td>
<td>Simple and complex partial Generalized tonic-clonic</td>
<td>$</td>
</tr>
<tr>
<td>1 or 2 times daily</td>
<td>10–20</td>
<td>Skin rash (5%–10%, rarely serious), liver enzyme elevation, blood dyscrasias, gingival hyperplasia, dose-related encephalopathy</td>
<td>Generalized tonic-clonic Simple and complex partial</td>
<td>$</td>
</tr>
<tr>
<td>2 times daily</td>
<td>5–15</td>
<td>Skin rash (5%), depression, diminished libido</td>
<td>Simple and complex partial</td>
<td>$</td>
</tr>
<tr>
<td>2 to 4 times daily</td>
<td>5–70</td>
<td>Dizziness, asthenia, weakness</td>
<td>Simple and complex partial</td>
<td>$$$</td>
</tr>
<tr>
<td>1 or 2 times daily</td>
<td>2–25</td>
<td>Cognitive problems, kidney stones, weight loss, headache, fingers/toes paresthesia</td>
<td>Generalized tonic-clonic Simple and complex partial Lennox-Gastaut syndrome</td>
<td>$$</td>
</tr>
<tr>
<td>1 or 2 times daily</td>
<td>10–40</td>
<td>Skin rash, cross-reacts with sulfonamides, somnolence, depression, kidney stones, blood dyscrasias, oligohidrosis and hyperthermia in children</td>
<td>Simple and complex partial Generalized tonic-clonic Myoclonic Absence</td>
<td>$$</td>
</tr>
</tbody>
</table>
practitioners be familiar with the rules in their state. Details about the various regulations are available from the state motor vehicle department and are summarized on the Epilepsy Foundation Web site (www.epilepsyfoundation.org). Only a handful of states require that physicians report individuals with seizures to the motor vehicle department but most require that physicians inform patients of the rules particular to their jurisdiction.

At times it is prudent to place restrictions on patients in the workplace, such as when operating machinery. However, individuals do not necessarily need to disclose medical problems to their employer. The Americans with Disabilities Act is a federal civil rights law that prevents discrimination against individuals in the workplace and under other circumstances on the basis of their medical problems. Details about this legislation are available at the U.S. Department of Justice Web site (www.ada.gov).

Many patients will inquire about restrictions in regard to recreational activities. There are no general rules about restrictions that must be placed on individuals with seizures. However, special care around water, heights, and dangerous equipment is an appropriate admonition. Other restrictions should be carefully individualized. Finally, many individuals and their families will want additional information about seizures. They can be referred to the Epilepsy Foundation or local affiliates for further information and identification of resources in their communities.

2 Months Later

At the follow-up visit, the patient reports that she has tolerated the medication without side effects and has had no further seizures, either generalized or partial. 

- When can the patient be considered for withdrawal from AEDs?

An important role for the primary physician or consultant neurologist (and one that is frequently and unfortunately overlooked) is in the evaluation for withdrawal from AEDs. Numerous studies have suggested that over 70% of patients with epilepsy will enter long-term remission [5,29]. At least 50% of patients who go untreated may spontaneously remit [30]. These findings suggest that there may not be a need for long-term AED treatment. There are a number of reasons that medication withdrawal should be considered, including side effects, social considerations, and cost. Typically, patients who have been completely seizure-free for a period of 2 years should be considered as potential candidates for withdrawal from medication. The consulting neurologist is well equipped to discuss the possibility of relapse based on age, seizure type, and other factors and can obtain an EEG, which has been demonstrated to offer important prognostic information [31,32]. A normal EEG suggests a favorable prognosis in regard to safely coming off medication, whereas epileptiform abnormalities suggest a poor prognosis. Once the decision to withdraw the medication has been made, the consultant can counsel the patient and their family on how to safely taper the medication and what to do if there is a relapse. There are currently no legal guidelines regarding driving or operating potentially dangerous machinery while undergoing withdrawal from medication, but most neurologists would advise a period of time off from these activities.

- When is referral to a neurologist or epilepsy center warranted?

If adequate (ie, complete) seizure control is obtained, no further specialty evaluation may be warranted. However, if seizures persist and cannot be brought under control by the primary care physician within 3 months, the neurologist should then assume responsibility for managing the patient’s seizures [33]. Once the seizures are controlled, care can be transferred back to the primary care physician. It is important to recognize that the (initial) diagnosis of epilepsy may be erroneous. If the diagnosis is in question or if nonepileptic events are suspected, early referral to a specialized epilepsy center is appropriate for diagnostic purposes. Outcomes are clearly better following early diagnosis of nonepileptic events [34]. Further, there is evidence that expert evaluation shortly after the onset of epilepsy likewise

| Table 4. Risk of Birth Defects Associated with Antiepileptic Drugs |
|------------------------|------------------------|
| **Category D**         | **Category C**         |
| Carbamazepine          | Felbamate              |
| Phenobarbital          | Gabapentin             |
| Phenytoin              | Lamotrigine            |
| Primidone              | Levetiracetam          |
| Valproate              | Oxcarbazepine          |
| Tiagabine              | Topiramate             |
| Zonisamide‡            |                       |

*Medications definitely associated with teratogenesis.
†Medications without enough evidence to say they are definitely safe but no evidence of teratogenesis.
‡Zonisamide has been associated with teratogenesis when used as polypharmacy with known teratogens but not when used as monotherapy.
improves outcome [35]. Early and accurate diagnosis as well as early therapeutic intervention with the best medication for the individual patient may minimize the number of seizures, reduce the number of antiepileptic drug trials, and minimize the impact of the seizures on the patient’s quality of life [35]. Because of this, it may be worth considering referral to a specialized epilepsy center early in the evaluation process even if the local general neurologist is reasonably confident that the diagnosis is correct.

The primary care physician has an important role in advocacy on behalf of their patients in the referral process from the general neurologist to the specialized epilepsy center. Recent evidence suggests that up to 70% of patients will have their seizures fully controlled with medication [36]. However, it also shows that only a small percentage of patients in whom the first AED was ineffective would ever become seizure-free with additional medical treatment. The authors concluded that patients who did not respond to initial medical therapy likely had refractory epilepsy that would persist despite trials of newer medications. In light of this finding, it is difficult to justify the amount of time (often 20+ years) that some individuals have seizures while medications are tried. Other authors have suggested that continued seizures despite adequate trials of 3 or more AEDs (used either alone or in combination therapy) is a practical way to define medically intractable epilepsy [37]. Many epilepsy centers have developed similar criteria for evaluating patients for possible surgical intervention.

It is important to get the individual patient the appropriate type and level of care they need. This can be controversial at times, particularly if the patient is concurrently under the care of a general neurologist. As in all cases, that which is in the best interest of the patient must take precedence. Less controversial are referrals to specialized epilepsy centers for acutely ill patients with uncontrolled seizures, status epilepticus, or patients with a seizure focus adjacent to eloquent cortex. In such cases, delaying or denying a referral to an epilepsy specialist can be detrimental to the patient’s health, safety, and quality of life.

### What are treatment options if seizures persist despite trials of medication?

When a patient has seizures that are refractory to medication, referral to a specialized epilepsy center for evaluation for epilepsy surgery is appropriate. A National Institutes of Health consensus conference recommended evaluation for surgery when seizures are not brought under adequate control with the resources available to the treating physician [38]. While the notion of brain surgery may sound radical, it should be weighed against the possibility of becoming totally seizure-free. The role of the neurologist or epileptologist is to lead the patient through the evaluation for epilepsy surgery. Prolonged video-EEG monitoring is the gold standard for assessing an individual’s seizures. This modality often allows for characterization of a patient’s seizures and localization of a seizure focus, if one exists. This technique is complemented by other studies, including MRI, positron emission tomography, or single photon emission tomography, neuropsychological testing, and the intracarotid amobarbital test (Wada test). When the findings from different studies are concordant (ie, all data point to a similar source such as one or the other temporal lobe) for the neurologic dysfunction(s), resective surgery can often be recommended. Discordant results may lead to further video-EEG evaluation with invasive electrodes (subdural strips or depth electrodes) to definitively localize the seizure focus. Table 5 shows seizure outcomes with different surgical procedures [39]. It is important for primary physicians to realize that brain surgery is an accepted method for treating epilepsy, even though it is grossly underutilized.

When the patient is not a good candidate for resective surgery or does not want brain surgery, consideration should be made for vagus nerve stimulation (VNS) therapy. This therapy has been available in the United States since 1997. Much of the preclinical and clinical data that led to its approval is summarized elsewhere [40]. While VNS is an alternative to both medication and surgical therapy, it is not generally considered curative. Rather, patients who receive VNS therapy can have a reduction in seizure frequency without the side effect profile of medications (VNS has negligible cognitive side effects) and without the risks of brain surgery [40]. Patients report improvements in their global sense of well-being with VNS [40]. Because the VNS apparatus is active intermittently throughout the day, compliance is

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of Patients</th>
<th>Seizure-Free %</th>
<th>Improved, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior temporal lobectomy</td>
<td>3579</td>
<td>68</td>
<td>24</td>
</tr>
<tr>
<td>Amygdalohippocampectomy</td>
<td>413</td>
<td>69</td>
<td>22</td>
</tr>
<tr>
<td>Neocortical resection (nontemporal)</td>
<td>805</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>Lesionectomy</td>
<td>293</td>
<td>67</td>
<td>22</td>
</tr>
<tr>
<td>Hemispherectomy</td>
<td>190</td>
<td>67</td>
<td>21</td>
</tr>
<tr>
<td>Multilobar resection</td>
<td>166</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>Corpus callosotomy</td>
<td>563</td>
<td>8</td>
<td>61</td>
</tr>
</tbody>
</table>

not a concern. The device also can be activated manually via a hand-held magnet, giving patients and their families a sense of empowerment over their disorder. The decision to undergo the surgical implantation of VNS is one that a patient should make in conjunction with a neurologist. Following device implantation, the neurologist will be responsible for adjusting the stimulation parameters and individualizing them for the patient.

Conclusion

Primary care physicians play a vital role in the treatment of individuals with seizures or epilepsy. Many patients with a single seizure or with recurrent seizures (epilepsy) can be safely and appropriately managed in the primary care setting. In conjunction with a consulting neurologist, the primary care physician can effectively evaluate the patient, select medication when appropriate, and monitor treatment. When seizures persist despite appropriate treatment(s), a neurologist will likely take a more active role in management. Referral to a specialized epilepsy center and consideration for epilepsy surgery should be done early in the treatment course for appropriate patients. Collaboration is key in achieving the goal of no seizures and no side effects.

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Author contributions: conception and design, MRT, DML; drafting of the article, MRT, GLA, DML; critical revision of the article for important intellectual content, MRT, GLA, DML.

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23. Alsdorf RM, Wyszyński DF, Holmes LB, Nambisan M. Evidence of increased birth defects in the offspring of women


1. What is the most appropriate approach to deciding whether to initiate treatment following a single seizure?
   (A) Patients should always receive treatment
   (B) Due to the low risk of recurrence, treatment is not needed
   (C) The decision to treat should be based on the likelihood of recurrence in that individual

2. Once a patient has a second seizure, the likelihood of recurrence is great and therefore he/she should be placed on antiseizure medications.
   (A) True
   (B) False

3. When treating a woman of childbearing age, which of the following is true?
   (A) All of the antiepileptic medications are equally teratogenic
   (B) There is a greater than 90% likelihood of a good outcome of the pregnancy
   (C) The patient should be advised to not get pregnant

4. What is necessary to make a definitive diagnosis of epilepsy?
   (A) Recurrent seizures
   (B) Epileptiform abnormalities on electroencephalogram
   (C) Magnetic resonance imaging abnormalities
   (D) All of the above

5. When a patient with epilepsy does not respond to medication therapy, it may be due to which of the following?
   (A) Subtherapeutic dosing of an appropriate medication
   (B) Inappropriate medication for that seizure type
   (C) Wrong diagnosis (ie, the patient does not have epilepsy)
   (D) They are truly medically refractory
   (E) All of the above
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6. What topics would you like to see presented in the future?
   ___________________________________________________________
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