ABSTRACT

The population of newly diagnosed elderly patients with epilepsy is growing rapidly. Epilepsy can be difficult to diagnose because there are numerous conditions that can generate a similar symptomology. The average time to diagnosis for some groups of elderly patients is several years. A reliable medical history and descriptions of seizure activity from reliable witnesses are among the more important diagnostic clues. Laboratory tests can distinguish between various alternative diagnoses, whereas imaging techniques can uncover brain lesions that may be responsible for seizure activity. Management of the condition is complicated by the psychosocial issues involved, the difficulty for the patient to physically comply with the treatment schedule, and the likelihood of side effects that impair cognition and memory. Additionally, the ability of other drugs to interact with and inadvertently alter the dose of the antiepileptic drug causes complications. Care must be taken in choosing the appropriate antiepileptic drug and in the dosing because comorbidities can have surprisingly large effects. The goal of treatment is to block seizure activity; however, this goal must be balanced with the possible side effects in order to maximize the quality of life for these patients.

(SEIZURES IN OLDER ADULTS)

The population of elderly individuals is defined as those 65 years or older.¹ According to the US Census Bureau, the elderly population grew from 3.1 million in 1900 to 35 million in 2000, and remains the fastest growing segment of the US population today. This population is also at the highest risk for new-onset seizures. In part, this is because of the increased likelihood of a condition favorable to the creation of a seizure focus as the individual ages. Stroke, head injury, and the onset of Alzheimer’s disease are examples. Common causes of seizure activity in elderly patients are shown in Table 1.² These seizures are unlikely to be isolated events. The recurrence rate for untreated elderly individuals who have experienced their first seizure is greater than 90%.³

Within the nursing home environment, it is estimated that 10% of patients are prescribed an antiepileptic drug (AED). The percentage of nursing home patients taking an AED specifically for epilepsy is 6%. The diagnosis and management of patients with epilepsy who live in the nursing home environment is complex. Elderly patients often have concurrent diseases that can mask the source of altered behavior. Because epilepsy has a wide spectrum of clinical presentations and there are numerous disease states that can mimic seizure symptomology, it is possible that the condition may be misdiagnosed.⁴

A second complexity derives from psychosocial issues. Unlike most other chronic diseases, such as asthma or hypertension, there is a significant social stigma associated with epilepsy.⁵ Epilepsy can reduce self-esteem, feelings of control, and quality of life. In younger individuals, this can manifest as an inability to find employment. In the elderly patient with epilepsy, there is the added issue of a more prolonged post-ictal state, resulting in impaired cognition and an increased number of falls, causing bone fractures, bruises, and dislocations.

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(SEIZURES IN OLDER ADULTS)
There are complexities associated with AED therapy. It is well understood that elderly patients have altered drug pharmacokinetics and pharmacodynamics. Additionally, the presence of other drugs used to treat concurrent illnesses can lead to complex drug interactions. Also, deteriorating memory and poor motor function can interfere with compliance.

**DEFINITION OF TERMS**

Given the complexities associated with the diagnosis of epilepsy, it is critical to provide exact definitions of the terms commonly used to describe this syndrome. The 3 main terms used are seizure, convulsion, and epilepsy.

**Seizure** is defined as any abnormal electrical discharge involving hypersynchrony of brain neurons. A seizure may be purely electrical in nature, with little or no observable behavioral component, and may involve deep brain structures. The location of this abnormal hypersynchronous neuronal discharge clearly affects the seizure presentation. Seizure activity within neurons of the motor cortex will most likely produce convulsive movements, whereas seizure activity within the temporal lobe or frontal cortex will likely have profound sensory or cognitive effects. Because seizures result from a variety of potentially treatable conditions (eg, infections, electrolyte abnormalities, hypoglycemia), it is possible to have seizures and not have epilepsy.

A **convulsion** is a specific type of seizure involving neurons of the motor cortex. A tonic-clonic seizure will involve convulsive behavior. Although the classic epileptic seizure is commonly associated with a convulsion, it is important to note that this represents a small subset of patients. Most patients with epilepsy present with seizures associated with cognitive or sensory components rather than seizures with convulsions.

Finally, the term **epilepsy** is reserved for the condition of experiencing 2 or more unprovoked seizures. The experience of a single seizure, even if well documented, does not necessarily indicate epilepsy because trauma, drug effects, or disease can provoke 1 or more seizures.

Seizures can be classified according to the region of brain involvement and according to their presentation, which can have motor, sensory, autonomic, or psychiatric components. Partial seizures involve a localized focus, involving only 1 hemisphere, whereas generalized seizures involve widespread neuronal activity involving both hemispheres. Partial seizures can be simple (without loss of consciousness) or complex (with loss of consciousness). A classic example of a complex partial seizure would involve an individual who, at the onset of the seizure, starts to exhibit abnormal behavior. This could involve something as subtle as the rubbing together of fingers, or the twitching of their lips. It could involve excessive movement such as walking or fiddling with an object. The seizure can begin as a localized focus in 1 hemisphere and then spread to involve both hemispheres in a process referred to as secondary generalization. These secondary generalized seizures almost always have a convulsive motor component.

Generalized seizures can be classified as tonic-clonic, absence, myoclonic, tonic, and atonic. Rather than slowly spreading, their neuronal activation pattern is virtually instantaneous. The tonic-clonic seizure is the most familiar form of generalized seizure. The patient loses consciousness, the body stiffens, and the patient falls to the ground. This is followed after several minutes by jerking movements, which then subside and the patient regains consciousness. The patient may appear lethargic afterward.

Absence seizures are most common in children and involve a brief loss of consciousness without the stiffening of the body. It is rarely observed in the elderly.

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**Table 1. Common Causes of Recent-Onset Seizures in Elderly People**

<table>
<thead>
<tr>
<th>Type</th>
<th>Causes</th>
</tr>
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<tbody>
<tr>
<td>Acute Symptomatic</td>
<td>Acute cerebral infarction, Head injury, Subarachnoid hemorrhage, Intracranial hemorrhage, Subdural hematoma, Metabolic disturbance, Alcohol withdrawal/drug related</td>
</tr>
<tr>
<td>Remote Symptomatic</td>
<td>Previous cerebral infarction, Head injury, Cerebral atrophy, Tumor, Cerebrovascular disease, Nonvascular dementia</td>
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</tbody>
</table>

Myoclonic seizures involve brief shocklike muscular jerks.

Tonic seizures also involve the muscles. In this case, the muscle tone is increased and the body stiffens.

Atonic seizures are, in a sense, the opposite of tonic seizures. The patient loses muscle tone during the seizure, resulting in the drooping of eyelids, nodding of the head, and the dropping of held objects. The patient often collapses to the ground.

In many cases, the patient is unaware that a seizure has taken place. Thus, if the event was unobserved, it could go completely unnoticed. However, given that seizures are often accompanied by abnormal events, the occurrence of these events can serve as a clue that seizure activity has occurred. Episodic events that are associated with seizure activity include falls, incontinence, movement disorders, memory loss, abnormal behaviors, and loss of attention. These events are associated with many different pathologies and, as such, serve only as suggestive clues.

DIAGNOSIS OF EPILEPSY IN THE ELDERLY

The possibility of misdiagnosis of an elderly patient who has demonstrated behavior consistent with epilepsy is high. Perhaps the most valuable initial information is a reliable personal and family medical history, in addition to a written narrative by a witness who has observed the event.2 The witness should be queried about pallor and cyanosis, in addition to behaviors such as abnormal movements, tongue biting, urinary incontinence, and evidence of impaired consciousness. Postictal symptoms include confusion, headache, drowsiness, and Todd’s paralysis (ie, unilateral muscle weakness). The number of disease states with epilepsy-like symptoms is great and a partial list is given in Table 2.6 Several of these conditions can be differentiated by standard laboratory tests.

Electroencephalography (EEG) recordings are often thought of as definitive measures of epileptiform neuronal activity. However, it is a surprisingly poor diagnosis tool in the elderly and should be interpreted with caution.7 As many as 38% of healthy older adults have abnormal EEG patterns and, interestingly, relatively few elderly patients with seizures have abnormal interictal EEGs.8 However, an EEG recording during a seizure episode is useful as a means to classify the seizure type.

Neuroimaging techniques are showing promise as diagnostic tools. Magnetic resonance imaging (MRI) is currently the procedure of choice for the identification of potential neural lesions.9 Although computed tomography scans are useful when MRI is unavailable, MRI is superior to computed tomography scans in the ability to identify intracerebral lesions.7 It has been estimated that underlying abnormalities can be detected with 80% accuracy by this method.

EPIDEMIOLOGY OF EPILEPSY

It is estimated that between 2% and 4% of the US population has active epilepsy at any one time, and 1 out of 10 individuals will experience a seizure at some point in his life. Thus, epilepsy is far more common than previously recognized. Once considered a disease of childhood, over the past 15 years, it has become recognized that the pattern of seizure onset is bimodal: one peak occurring in the very young and another peak occurring in individuals greater than 65 years of age.10 The Figure illustrates this point by showing incidence rates for the various seizure types as a function of age. Whereas myoclonic and absence seizures are primarily diseases of early childhood, partial and generalized tonic-clonic seizures primarily affect the older population.

### Table 2. Conditions that May Be Mistaken for Epilepsy

<table>
<thead>
<tr>
<th>Conditions that May Result in Apparent Alteration or Loss of Consciousness</th>
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<tbody>
<tr>
<td>Syncope</td>
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<tr>
<td>Transient cerebral ischemia</td>
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<tr>
<td>Metabolic disorders (eg, hypoglycemia)</td>
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<tr>
<td>Migraine</td>
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<tr>
<td>Psychiatric conditions</td>
</tr>
<tr>
<td>Drug effects</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions that May Present with Motor or Sensory Disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient ischemic attacks</td>
</tr>
<tr>
<td>Movement disorders</td>
</tr>
<tr>
<td>Vestibular disturbances</td>
</tr>
<tr>
<td>Sleep disorders</td>
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<table>
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<tr>
<th>Conditions that May Cause Drop Attacks</th>
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<tbody>
<tr>
<td>Vascular insufficiency</td>
</tr>
<tr>
<td>Vestibular disorders</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Postural instability in the elderly</td>
</tr>
</tbody>
</table>


More than 65,000 elderly patients are diagnosed with new-onset seizures each year, resulting in an incidence rate of 60 to 150 per 100,000 individuals. In part, this is a consequence of increased survival. As the baby boomer population ages, it is estimated that by 2025, more than 50% of new-onset seizures will occur in older adults. As shown in Figure 1, more than 70% of new-onset seizures in elderly patients can be classified as partial seizures. Approximately 35% of these new onset seizures will be status epilepticus (ie, a prolonged seizure lasting more than 10 minutes), which can be life threatening.

**Clinical Presentation**

Epilepsy presents quite differently in young versus older adults. As aforementioned, the most common seizure type for older adults is the partial seizure, whereas children more often experience generalized seizures. Partial seizures are characterized by altered behavior, such as confusion, disorientation, and unresponsive staring. During the seizure period, the patient may exhibit orofacial automatisms, rubbing or tapping of fingers, stroking, wandering, or disrobing. After the seizure, the patient is in a state of confusion that can last from hours to days. Because these abnormal behaviors can have other causes, the need for a thorough workup is important.

Often, patients with epilepsy experience a somatic sense of an altered state preceding the seizure, which has been termed the *aura*. In elderly patients, this sensation is much diminished as compared with younger patients. Similarly, automatisms (nonpurposeful movements) that are often observed in younger patients with epilepsy are less frequently observed in older patients. Also, the postictal period can be quite lengthy in older patients, whereas younger patients generally recover within several hours. In general, the seizure frequency in younger patients is significantly higher than that seen in older patients. However, the potential for injury in older patients is significantly higher than that for younger patients.

**Causes of Epilepsy**

Unfortunately, most cases of epilepsy are still of unknown or idiopathic etiology. For those cases of epilepsy in which the cause is known, it is worth noting that the etiology appears different in the young versus the older population (Table 3).  

Cerebrovascular conditions are the single most commonly identified cause of epilepsy in older patients.  

It has been estimated that 4% to 14% of cerebral infarctions are associated with seizures in the first 1 to 2 weeks. Greater than 10% of infarctions are associated with seizures at a later time point subsequent to the insult.

It is not widely recognized that patients with Alzheimer’s disease are also at an increased risk for seizures; however, 10% to 20% of these patients will have a seizure within 5 years. Brain tumors are also possible causes for seizure activity. In addition to underlying damage caused by disease or trauma, therapies used to treat other disease states can induce
seizures. Generally, these drugs induce seizures by inadvertently lowering the seizure threshold. Examples of commonly prescribed drugs that have been associated with increased seizure activity in elderly patients include: opioid analgesics (especially meperidine), beta-lactam and quinolone antibiotics, bupropion, theophylline, antipsychotic drugs (especially clozapine and phenothiazines), and isoniazid. Additionally, the sudden withdrawal of the individual from an abused drug such as benzodiazepines, barbiturates, or alcohol can also induce seizures.

**TREATMENT OF EPILEPSY**

The goal of therapy is to have no seizures and no side effects. A patient's quality of life is strongly dependent on both factors. Because all AEDs have side effects, some of which are quite serious, there must be a balance created between these 2 parameters. This point is not often appreciated by prescribing physicians.

The first AED to be introduced almost a century ago was phenobarbital. This was followed in subsequent decades by phenytoin, primidone, ethosuximide, diazepam, carbamazepine, and valproate. These are considered the first-generation AEDs. The efficacy of phenobarbital, phenytoin, carbamazepine, and valproate was determined in the large prospective Veterans Administration clinical trials, VA-I and VA-II. In general, these drugs were differentiated by their side effects. The following study observations were of particular importance to the treatment of the elderly patient with epilepsy: (1) In VA-I, carbamazepine was superior to phenytoin in the incidence of cognitive side effects. (2) In VA-II, carbamazepine was superior to valproate at controlling partial seizures, and had fewer long-term side effects such as weight gain, hair loss, and tremor.

During the past decade, an additional 9 AEDs have been approved by the US Food and Drug Administration, including felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide, and pregabalin. Felbamate usage was curtailed after the first year of use because of an association with aplastic anemia and liver failure. However, the other 8 drugs show significant improvements in safety and decreased side effects as compared with first-generation AEDs.

In general, cognitive impairment, including memory deficits, attention deficits, and mental slowing, is a frequently occurring secondary consequence of AED therapy. Phenobarbital has dramatic effects on cognition, whereas phenytoin, carbamazepine, and valproate cause a general psychomotor slowing. Attempts to increase efficacy by polytherapy enhances this effect.

Side effects from second-generation AEDs are not well studied in the elderly at this time. Topiramate is associated with cognitive impairment, whereas gabapentin, tiagabine, levetiracetam, and pregabalin are associated with mood alterations. Interestingly, lamotrigine has been shown to have a positive effect on cognition. Efficacy among these drugs is roughly the same, with the caveat that different drugs are more efficacious for certain seizure types. Ethosuximide, for example, is used for absence seizures and is a poor choice for partial seizures. First-line therapeutic choices for partial seizures include carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, pregabalin, phenytoin, and zonisamide. Targets for these drugs include the inhibition of the voltage-sensitive sodium and calcium channels, which mediate the action potential, potentiation of GABAergic (inhibitory) neurotransmitters, and inhibition of glutamate (excitatory) neurotransmitters. Different drugs affect different combinations of these targets.

Identifying the appropriate AED for an elderly patient involves many parameters that can be quite different from younger patients. For example, teratogenicity and interaction with oral contraceptives will not be issues. Importantly, given the greater possibility of poor renal or liver function, high doses of AEDs such as phenytoin should be avoided. Altered function in these organs can also affect pharmacokinetic profiles, making dosing challenging. Also, comorbidities such as depression or anxiety may be present and need to be considered in AED selection. Some AEDs exacerbate depression, whereas other AEDs may treat the condition in addition to epilepsy.

**CONCLUSIONS**

Epilepsy, once considered a condition that begins primarily in childhood, is becoming recognized as a condition that can also begin in the elderly. New cases of epilepsy will continue to increase as the elderly population continues to grow. Importantly, the causes and clinical presentation of epilepsy in the young and old populations are quite different. Many of the signs and symptoms of seizure activity are shared by other infirmities associated with aging, making it possible to mis-
diagnose the condition. Management of the disease is complicated by psychosocial factors, the presence of comorbidities, and the potentially serious consequences of AED side effects. Although the goal of AED therapy is to completely block seizure activity, this is often accompanied by a significant deterioration in quality of life because of the onset of side effects. A critical function of the consulting pharmacist is to attempt to balance these 2 issues to maximize quality of life in patients.

REFERENCES