Seizure Disorders in the Elderly

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Seizure disorders become increasingly common after the age of 60 years and can have a significant impact on functional status. The goal of antiepileptic drug therapy is to control seizures but preserve quality of life. If possible, seizure control should be achieved with one agent given in the lowest effective dosage. Clinical response, rather than drug levels, should guide dosage changes. All antiepileptic drugs can cause dose-dependent sedation and cognitive impairment. Although the newer agents may have theoretical advantages over standard antiepileptic agents, higher cost may limit their use. Drugs for first-line monotherapy of seizures in elderly patients include carbamazepine, valproic acid, oxcarbazepine, gabapentin, and lamotrigine. (Am Fam Physician 2003;67:325-32. Copyright© 2003 American Academy of Family Physicians.)

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The general perception is that seizures occur most often in infants but rarely in older adults. However, population-based studies indicate that seizure disorders increase in incidence and prevalence after the age of 60 years.[1,2] Because people are living longer and becoming more likely to have concurrent medical illnesses requiring multiple medications, family physicians are increasingly challenged to provide appropriate management of seizures and monitoring of antiepileptic drug therapy in their older patients. This article reviews the epidemiology, etiology, and diagnosis of seizure disorders in the elderly. An approach to antiepileptic drug selection is suggested.

Epidemiology, Classification, and Etiology

Epidemiologic studies consistently document an increased incidence of seizure disorders in older adults and suggest that aging is a definite risk factor.[3] In the United States, the annual incidence of seizures is approaching 100 seizures per 100,000 persons over 60 years of age.[4] Epilepsy, a chronic condition characterized by recurrent and usually spontaneous seizures, affects 1.5 to 3 million people in the United States.[4]

Epilepsies and epileptic syndromes are currently classified as localized (partial or focal) or generalized, based on clinical and electroencephalographic changes *(Table 1)*.[5] A generalized epilepsy or epileptic syndrome results in seizures that involve the cerebral hemispheres bilaterally and symmetrically at the time of onset. In contrast, a partial epilepsy produces seizures that originate in a specific region of the cerebral cortex. The seizures may be associated with signs or symptoms peculiar to their region of origin, and they may occur with or without mental status changes or loss of consciousness. Partial epilepsy, the most common type of epilepsy in the elderly, is often the result of localized cortical dysfunction.

In many older patients, an underlying cause of seizure activity is clearly identifiable. Epidemiologic studies have defined acute symptomatic seizures as those that happen in the context of an acute insult to the central nervous system (CNS) or during an acute metabolic disturbance.[3,6] These seizures are associated with subdural hematoma, stroke, and CNS infection. They also can occur with systemic metabolic conditions such as uremia, hyperglycemia, hypoglycemia, hyponatremia, and alcohol withdrawal.

A five-year study[7] of 151 patients with a first seizure after 60 years of age found that 32 percent of the seizures were caused by strokes and 14 percent by brain tumors, including meningiomas, malignant gliomas, and brain metastases; 25 percent had no identifiable cause. A community cohort study[8] of 675 patients with a first stroke found that the risk of having a seizure was 2 percent at stroke onset and 11 percent in the first five years after the

See page 237 for definitions of strength-of-evidence levels.

Seizures in the elderly may be caused by stroke, systemic metabolic conditions, subdural hematoma, central nervous system infection, degenerative disorders, or malignancy. The seizures also can be idiopathic.

stroke. Seizure recurrence after a stroke can be immediate, or it may not happen for several years.[9] Recurrences are more common after hemorraghic or severe ischemic strokes with cortical (particularly occipital) involvement and late onset of the first seizure.[8,10]

Of the degenerative disorders, Alzheimer's dementia and amyloid angiopathy are known major causes of seizures.[11] Advanced Alzheimer's disease has been identified as a risk factor for new-onset generalized tonic-clonic seizures in older adults.[12] It is associated with a 10 percent prevalence of seizures, particularly late in the illness.[11] An increased prevalence of seizures also has been documented with other types of dementia.[11]

Status epilepticus has been defined as a single generalized seizure lasting more than five minutes or a series of seizures lasting longer than 30 minutes without the patient regaining consciousness. The greatest increase in the

TABLE 1
Classification of Epilepsies and Epileptic Syndromes

Localized (partial or focal)	**Generalized**	**Undetermined**
Idiopathic (with age-related onset)	Idiopathic (age-related onset; listed in order of age)	Situation-related seizures
Benign childhood epilepsy with centrotemporal spike	Benign neonatal familial convulsions	Febrile convulsion
Childhood epilepsy with occipital paroxysms	Benign neonatal convulsions	Isolated seizures or isolated status epilepticus
Primary reading epilepsy	Benign myoclonic epilepsy in infancy	Seizures occurring only when there is an acute metabolic or toxic event because of alcohol, drugs, eclampsia, nonketotic hyperglycemia, or other factors
Symptomatic	Childhood absence epilepsy	
Chronic progressive epilepsia partialis continua of childhood	Juvenile myoclonic epilepsy (impulsive petit mal epilepsy)	
Syndromes characterized by seizures with specific modes of presentation	Epilepsy with grand mal seizures on awakening	
Temporal lobe epilepsies	Other generalized idiopathic epilepsies not defined above	
Frontal lobe epilepsies	Epilepsies with seizures precipitated by specific modes of activation	
Parietal lobe epilepsies	Cryptogenic or symptomatic (age-related onset; listed in order of age)	
Occipital lobe epilepsies	West's syndrome	
Cryptogenic (presumed to be symptomatic, with unknown etiology)	Lennox-Gastaut syndrome	
	Epilepsy with myoclastic-astatic seizures	
	Epilepsy with myoclonic absences	
	Symptomatic	
	Nonspecific etiology	
	Early myoclonic encephalopathy	
	Early infantile encephalopathy with suppression burst	
	Other symptomatic generalized epilepsies not defined above	
	Specific syndromes	
	Diseases in which seizures are a presenting or predominant feature*	

**—Epileptic seizures may complicate many disease states.*

Adapted with permission from Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30:389-99.

incidence of status epilepticus occurs after the age of 60 years.[13] The most dramatic clinical presentation is generalized convulsive seizures. Nonconvulsive seizures may cause sudden changes in behavior and cognition.

A study[14] of 342 patients with status epilepticus who had their first seizure after 60 years of age found that cerebrovascular disease was the leading cause, followed by head trauma. Status epilepticus also can occur because of hypoxia, hyperglycemia, intracranial infection, brain tumors, and drug intoxication or withdrawal.

In patients with status epilepticus, the immediate goals are to stop the seizure and support cardiopulmonary function. Once these goals are accomplished, treatment of possible causes and precipitants (e.g., intracranial infection, hyperglycemia) is indicated.

Diagnostic Evaluation

The first step in diagnosing the cause of a seizure is to obtain a moment-by-moment description of the event from a witness. When more than one event clearly recognizable as a seizure has occurred, the diagnosis of epilepsy is made.

If the diagnosis of epilepsy is established, a careful search for predisposing factors is indicated. A detailed medical history should be obtained from the patient and family members. It is important to inquire about the patient's current habits (e.g., possible substance abuse), a history of seizures, and the presence of risk factors (e.g., head trauma, cerebrovascular disease). A systematic review of systems should include questions about possible sleep disorders. A careful review of current medications, including over-the-counter agents, is essential, because some drugs used to treat common geriatric problems may lower the seizure threshold. Finally, the physical examination should include a thorough neurologic assessment.

The initial laboratory evaluation of possible acute symptomatic seizures should include: a complete blood count; electrolyte, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, and glucose levels; an erythrocyte sedimentation rate; liver function tests; serologic tests; a chest radiograph; and an electrocardiogram. When appropriate, serum drug levels and a toxicology screen should be obtained.

A detailed cardiovascular evaluation is often required in the patient with suspected cardiogenic syncope, transient ischemic attack, or stroke. The work-up often might include an echocardiogram, Holter monitoring, and carotid Doppler ultrasonography. Acutely, computed tomographic scanning of the brain may exclude hemorrhage. When feasible, magnetic resonance imaging is the neurodiagnostic study of choice because of its sensitivity to infarcts and focal gliosis. Lumbar puncture is not routinely required unless the patient is febrile or has recently had a fever, meningitis is suspected, or the patient is immunocompromised.

Electroencephalography can help to establish the diagnosis of epilepsy and classify the seizure type. When possible, an electroencephalogram (EEG) should be obtained to assess prognosis and select appropriate drug therapy. Elderly patients can have episodes that mimic seizures but are actually the result of syncope, a sleep disorder, or a psychiatric illness.[15] Older adults without epilepsy generally have no significant background changes on their EEG. A study[16] comparing changes on EEGs in young patients (20 to 59 years) and older patients (over 60 years of age) who had epilepsy found decreased background rhythm, rhythmicity, and amplitude in the older group. Temporal lobe abnormalities were common in both groups, but frontal lobe discharges and slow waves were seen significantly more often in the older patients.

If the diagnosis is uncertain, inpatient monitoring may be indicated. A recent retrospective review[15] of 18 older adults who were admitted to an epilepsy-monitoring unit at a university hospital found that three patients who were receiving antiepileptic drug therapy

TABLE 2
Antiepileptic Drugs Recommended for Use in the Elderly

Drug	*Indication*	*Dose-related toxicities*	*Idiosyncratic side effects*	*Advantages*
Older drugs				
Phenytoin (Dilantin)	Partial seizures (simple and complex), generalized seizures	Ataxia, nystagmus, diplopia, confusion, sedation, lethargy, blurred vision	Blood dyscrasias, rash, hepatoxicity, Stevens-Johnson syndrome, neuropathy, lymphadenopathy, pancreatitis, osteomalacia, osteoporosis, folate deficiency	Low cost
Valproic acid (Depakene)	Generalized seizures, absence seizures, myoclonic seizures, partial seizures (simple and complex), migraine prophylaxis, mania	Tremors, diarrhea, somnolence, sedation, lethargy, minor hepatic enzyme elevation, nausea, vomiting, ataxia	Pancreatitis, rash, thrombocytopenia, blood dyscrasia, Stevens-Johnson syndrome, weight gain, osteoporosis	Broad-spectrum efficacy
Carbamazepine (Tegretol)	Partial seizures (simple and complex), generalized seizures, trigeminal neuralgia	Diplopia, dizziness, ataxia, drowsiness, hyponatremia, nausea, headache	Hyponatremia, cardiac conduction problems, morbilliform rash, agranulocytosis, aplastic anemia, Stevens-Johnson syndrome, hepatic failure, serum sickness, osteomalacia, osteoporosis	Minimal sedation and cognitive adverse effects
Newer drugs				
Oxcarbazepine (Trileptal)	Partial seizures (simple and complex), generalized seizures, trigeminal neuralgia	Dizziness, nausea, vomiting, ataxia, diplopia, sedation, lethargy, hyponatremia, tremor	Hyponatremia, cardiac conduction problems, rash	Few drug interactions
Gabapentin (Neurontin)	Partial seizures (simple and complex)	Somnolence, fatigue, ataxia, dizziness, blurred vision, diplopia, nystagmus, peripheral edema, tremor, nausea, weight gain	Leukopenia	No hepatic metabolism, drug interaction only with antacids
Lamotrigine (Lamictal)	Partial seizures (simple and complex), generalized seizures	Dizziness, tremor, ataxia, diplopia, headache, somnolence, blurred or dimmed vision, nausea, vomiting, incoordination, insomnia	Stevens-Johnson syndrome, aplastic anemia, thrombocytopenia, rash, weight loss (occasional), neutropenia, pancytopenia	Interaction with antiepileptic drugs only (especially valproic acid derivatives)
Topiramate (Topamax)	Partial seizures (simple and complex), generalized seizures	Difficulty thinking or concentrating, impaired memory, confusion, dizziness, ataxia, nervousness, tremor, fatigue, depression, anorexia, weight loss, dyspepsia, diplopia, sedation, lethargy	Nephrolithiasis, paresthesias, narrow-angle glaucoma (blurred vision, periorbital pain)	Interaction with antiepileptic drugs only
Tiagabine (Gabitril)	Partial seizures (simple and complex)	Dizziness, sedation, lethargy, tremor, nervousness, emotional changes, possible confusion	Rash, paresthesias, possible nonconvulsive status epilepticus	None

**—Estimated cost to the pharmacist for 30 days of treatment at the lowest given dosage, based on average wholesale prices (rounded to the nearest dollar) in Red book. Montvale, N.J.: Medical Economics Data, 2002. Cost to the patient will be higher, depending on prescription filling fee.*

Adapted with permission from Lackner TE. Strategies for optimizing antiepileptic drug therapy in elderly people. Pharmacotherapy 2002;22:332.

did not, in fact, have seizures. Five of the 18 patients had seizures, and the remaining 10 patients (eight of whom had previously been treated with antiepileptic drugs) had diagnoses other than epilepsy.

Antiepileptic Drug Selection

In general, all antiepileptic drugs have significant drug interactions, depend on gastrointestinal absorption, and may cause cog-

Disadvantages	*Representative geriatric maintenance dosage*	*Cost of brand name drug)**
Many drug interactions and food/nutrient interactions	200 mg per day	$ 18
Extensive protein binding, multiple drug interactions (e.g., with phenytoin)	500 mg once to three times daily	113
Ataxia, diplopia, multiple drug interactions	400 mg twice daily	61
None	600 mg twice daily	194
Dosage modification in renal disease, three times daily dosing	300 mg three times daily	116
Dosage modification in liver disease (?)	150 mg twice daily	169
Weight loss; dosage modification if creatinine clearance is <60 mL per minute (1 mL per second)	100 mg twice daily	195
Dosage modification in liver disease	32 mg per day	138

nitive side effects. Initial treatment of acute seizures requires antiepileptic drugs, whereas single seizures with a reversible precipitant do not require drug therapy.[17] Therefore, the first issue confronting the family physician is to decide whether a first single seizure requires treatment: Is the episode an isolated event or one that will require lifelong treatment? The fact that a large percentage of older adults will not experience another seizure episode makes a strong argument against treatment of a first single seizure. Candidates for antiepileptic drug therapy include patients with recurrent seizures, onset of epilepsy presenting as status epilepticus, or a clear structural predisposition for seizures.

It is estimated that broad use of the newer antiepileptic drugs would increase the annual cost of antiepileptic drug therapy in the United States from $25 million to more than $1.2 billion.[18] Few trials support the use of one antiepileptic medication over the others. Hence, the ideal antiepileptic drug is one with once-daily or twice-daily dosing, a low cost, minimal side effects, few or no drug interactions, low protein binding, little or no allergic or idiosyncratic reaction potential, and availability in a parenteral formulation.[19]

In general, it is advisable to "start low and go slow" with one agent. Results from the Veterans Affairs Cooperative Study[20] on the effects of age on epilepsy and its treatment indicate that compared with younger adults, older adults appear to be more responsive to antiepileptic drug therapy. However, they are also more likely to experience side effects at lower serum antiepileptic drug concentrations. Consequently, older adults usually require lower dosages and longer dosing intervals.[20] With any antiepileptic drug therapy, patients should be monitored closely for adverse effects, drug interactions, poor seizure control, and toxicity. Determination of the unbound drug concentration may be helpful when the clinical response appears inappropriate[21] or side effects are prominent.

Once the decision to treat is made, the next step is to determine whether to use a standard (older) antiepileptic drug or one of the newer agents *(Table 2)*.[22] The older antiepileptic drugs, which include phenytoin (Dilantin), valproic acid (Depakene), and carbamazepine

Few trials support the use of one antiepileptic drug over the others in elderly patients. Older agents are less expensive; newer agents sometimes have the benefit of fewer drug interactions or cognitive side effects.

(Tegretol), are less expensive than the newer agents and are considered appropriate selections for the initial treatment of seizures in older adults. In older adults, treatment with phenobarbital or primidone (Mysoline) is not widely recommended because of significant side effects, including sedation and drug-induced cognitive impairment.[1]

Newer antiepileptic drugs that are appropriate as first-line treatment in the elderly include oxcarbazepine (Trileptal), gabapentin (Neurontin), and lamotrigine (Lamictal). These agents have fewer drug interactions and better side effect profiles than the standard antiepileptic drugs. Because of serious hematologic and hepatic side effects, felbamate (Felbatol) is no longer generally recommended for use in older adults.[17]

PHENYTOIN

The absorption of phenytoin is altered by the physiologic changes of aging and by medications that affect gastrointestinal motility. For example, antacids and enteral feedings decrease the absorption and efficacy of the drug. Phenytoin is 90 percent protein bound; changes in protein binding caused by hepatic or renal disease result in a greater proportion of free or unbound drug, increasing the possibility of adverse events.

Because of the saturation kinetics of phenytoin, serum drug levels need to be monitored carefully. Small changes in the maintenance dosage lead to large changes in the total serum drug concentration.

The major advantages of phenytoin are low cost and the availability of an intravenous preparation for use in emergency situations. A liquid formulation is also available; however, the difficulty of maintaining phenytoin in suspension recommends against use of the suspension unless no other route or formulation is feasible. Drug interactions are common and are a major disadvantage to the use of phenytoin in older patients who are taking multiple medications.[23]

VALPROIC ACID

Valproic acid is highly protein bound. This drug is metabolized by cytochrome P450, fatty acid oxidation, and conjugation to active and inactive metabolites. Valproic acid levels may be decreased and phenytoin levels may be increased in patients taking both medications.

CARBAMAZEPINE

Carbamazepine is 65 to 85 percent bound to a combination of albumin and α_1-acid glycoprotein. The drug is metabolized in the liver, where it can induce its own metabolism and accelerate the oxidation and conjugation of other drugs. Because drug clearance is reduced in elderly people, carbamazepine levels should be monitored carefully, especially at the initiation of treatment.

The major advantages of carbamazepine include proven efficacy, twice-daily dosing in the elderly, and the availability of an extended-release preparation. However, hyponatremia and cardiac conduction problems may occur more often in older patients than in younger ones. Furthermore, carbamazepine interacts with a number of drugs.[23]

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OXCARBAZEPINE

Oxcarbazepine was recently labeled for use as monotherapy for partial-onset seizures in adults. Structurally related to carbamazepine and with a similar spectrum of activity, oxcarbazepine does not induce its own metabolism and has few drug interactions. Hepatic cytosolic enzymes metabolize the drug, with conversion to glucuronidase and subsequent renal excretion.

A recent multicenter, double-blind clinical trial[24] showed that oxcarbazepine is well tolerated and can be rapidly titrated over 14 days without compromising safety. In this trial, dizziness, fatigue, headache, somnolence, nausea, and vomiting were the most common side effects of the drug. Hyponatremia and cardiac disturbances remain clinically important problems.

No significant data are available on the use of oxcarbazepine in older adults. Theoretically, however, the drug has significant advantages.[25]

GABAPENTIN

Gabapentin is well absorbed and eliminated unchanged by the kidneys. The only known drug interaction is with aluminum-magnesium antacids, which decrease the absorption of gabapentin. Hence, gabapentin and these antacids should be administered at least two hours apart.

Of the newer antiepileptic drugs, gabapentin has the most favorable safety profile, although it can cause somnolence, dizziness, blurred vision, and leukopenia. Gabapentin may be recommended as initial monotherapy or add-on therapy for the treatment of seizure disorders in older patients who are taking multiple medications.[26] [Evidence level B, lower quality randomized controlled trial]

LAMOTRIGINE

Lamotrigine is weakly bound to plasma proteins and extensively metabolized by the liver, which is a significant advantage in patients with severe renal disease.[17] The drug is well tolerated by most patients.

The most common adverse effect of lamotrigine is a morbilliform rash that can develop during the first eight weeks of treatment. Slow titration minimizes the rash, which is usually mild and resolves when treatment is stopped. If lamotrigine needs to be discontinued, the dosage should be tapered over two weeks.

TOPIRAMATE AND TIAGABINE

Topiramate (Topamax) is weakly bound to proteins and not extensively metabolized. It is excreted primarily by the kidney. Tiagabine (Gabitril) is highly protein bound and extensively metabolized by the liver. Neither drug should be considered first-line therapy for seizure disorders in the elderly, because of the significant associated risk of personality changes or cognitive impairment.[17]

FOSPHENYTOIN

Current recommendations for the treatment of status epilepticus in older adults are similar to those in younger adults. Treatment is started with a benzodiazepine, preferably lorazepam (Ativan) because of its relative rapid onset of action and long half-life.[27] Next, fosphenytoin (Cerebyx) is given, and if the status epilepticus persists for more than 60 minutes, anesthesia is induced with pentobarbital, propofol (Diprivan), or midazolam (Versed).

Fosphenytoin is a safe and well-tolerated phenytoin prodrug that can be given intravenously with a lower risk of adverse effects (e.g., phlebitis, intravenous incompatibilities, hypotension, cardiac dysrhythmia) than parenterally administered phenytoin. Fosphenytoin also can be administered intramuscularly when intravenous access and cardiac monitoring are not available. Side effects are similar to those of phenytoin but occur less frequently. The prodrug is more expensive than phenytoin.

RECTAL DIAZEPAM

A recent randomized study demonstrated that the administration of a single dose of diazepam rectal gel (Diastat) was safe and effective in the treatment of homebound patients

who had repetitive seizures.[28] [Evidence level A, randomized controlled trial] Somnolence was the most frequent adverse effect. The drug appeared to have no observable depressive effect on respiratory rate.

Seizures and Motor Vehicle Operation

State driving laws must be reviewed carefully with the patient who has seizures and with the patient's family. Information about these laws can be obtained from the Epilepsy Foundation (www.efa.org) but should be verified by contacting the state Department of Motor Vehicles. Revocation of driving privileges, along with loss of independence, can have significant psychosocial implications for an elderly patient, especially when adequate and secure public transportation is not available or the patient's family cannot provide as-needed transportation.

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