Seizures in the elderly:
Nuances in presentation and treatment

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ABSTRACT

Acute symptomatic seizures and epilepsy are two of the most common neurologic complaints in the elderly. Stroke is the leading underlying etiology for both. Because clinical seizure manifestations in the elderly often differ from those in younger adults, they may be difficult to recognize or may be misdiagnosed. Interpretation of diagnostic tests in elderly patients with seizures is often complicated by comorbidities, and treatment decisions require careful consideration in the context of age-related physiologic changes, comorbidities, and the use of concomitant medications. Treatment of an acute seizure with a clear precipitating cause involves correcting the underlying etiology; antiepileptic drug (AED) therapy is generally reserved for patients with epilepsy (recurrent unprovoked seizures). The prognosis for elderly epilepsy patients treated with AEDs is generally good. Both older and newer AEDs are efficacious but have respective advantages and disadvantages; no ideal AED yet exists. Status epilepticus is a neurologic emergency that is particularly frequent in the elderly and associated with high mortality, although treatment can be effective.

KEY POINTS

The elderly have the highest incidence of seizures of any age group.

Nearly half of acute symptomatic seizures in the elderly and 30% to 50% of epilepsy cases in this age group are associated with stroke.

In the elderly, new onset of epilepsy is often associated with vague complaints such as confusion, altered mental status, or memory problems.

The differential diagnosis of seizures in the elderly should rule out spells due to other causes, such as syncope, transient ischemic attack, transient global amnesia, or episodic vertigo.

In treating epilepsy, the choice of antiepileptic drug (AED) is usually dictated by seizure type and tolerability and may be complicated by comorbidities or age-associated differences in AED pharmacokinetics.

Older and newer AEDs are both efficacious. Newer AEDs generally have better overall tolerability, fewer drug interactions, more predictable kinetics, and a broader spectrum of activity, but they also have slower titration schedules and cost considerably more than older AEDs.

The diagnosis and management of seizures and recurrent seizures (epilepsy) pose special challenges in the elderly. Seizures may present in elderly patients with nuances that are unique to this age group. Moreover, the treatment of seizures in the elderly is often complicated by concomitant medications and altered drug metabolism and excretion. Additionally, seizures threaten elderly patients' quality of life through potential injury and loss of independence, as well as through the side effects and costs of antiepileptic drugs (AEDs).

To explore these challenges and ways to address them, this article provides a general review of the diagnosis and management of seizures in patients aged 65 years or older, with a focus on the differential diagnosis

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of conditions with symptoms resembling seizures, the mechanism of seizures in older patients, the diagnostic work-up of elderly patients with suspected seizures, and the treatment of seizures in this population.

THE SCOPE OF THE CHALLENGE

The elderly are the fastest-growing segment of the general population. The US government predicts that by 2030 there will be 70 million adults over age 65 in the United States.[1] Whereas this segment made up 12.4% of the population in 2000, it will account for about 20% by 2030.[1] Figure 1 depicts the anticipated increased rate of growth of the elderly population.

The elderly have the highest incidence of seizures of any age group.[2] Older adults' increased risk for stroke, metabolic abnormalities, and comorbid conditions contributes to the frequency of seizures in this population. Thus, as the US population ages, physicians will increasingly face the challenge of diagnosing and effectively managing seizures in the elderly.

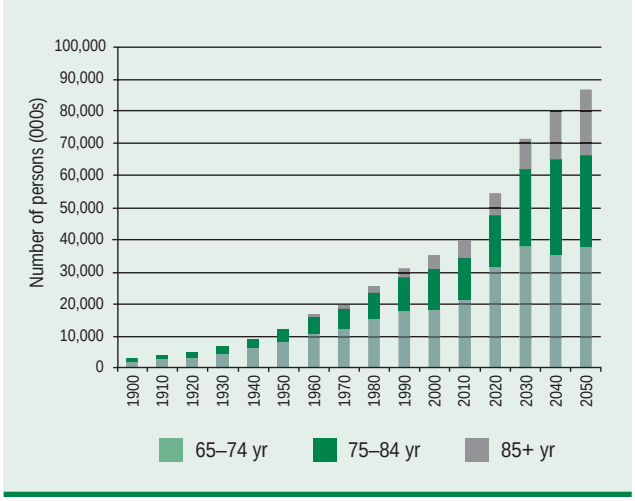

FIGURE 1. Older population of the United States by age, 1900 to 2050. US Bureau of the Census data (from reference 1).

DEFINITIONS: ACUTE SEIZURES VS EPILEPSY

Acute symptomatic seizures

Acute symptomatic seizures, or provoked seizures, occur in the context of an acute central nervous system (CNS) insult. The incidence of acute seizures in patients older than 60 years is approximately 100 per 100,000 population and increases with each decade of advancing age.[3–5]

Although drug withdrawal is the major cause of acute symptomatic seizures in adults aged 35 to 64 years, cerebrovascular disease is by far the most common cause of acute symptomatic seizures in the elderly, accounting for nearly half.[4] Most acute seizures occur within 24 hours of stroke onset.[6,7] Several studies of stroke patients have determined that 4% to 6% experience early seizures after a stroke.[7,8] Stroke type and location both play a role, with lobar location, hemorrhage, and anterior-hemisphere location associated with higher risk for early seizure.[7,8]

Other causes of acute symptomatic seizures in the elderly are trauma (responsible for 10.2% of cases), neoplasm (8.8%), and infection (2%).[3] Metabolic abnormalities, including hyponatremia, uremia, and hypocalcemia, are responsible for 10% to 15% of seizure cases in the elderly. Hyperglycemia or hypoglycemia related to insulin use can provoke seizures in elderly patients with diabetes.

Approximately 10% of seizures in the elderly are associated with alcohol or prescription drugs.[9] Commonly used drugs that are known to lower the seizure threshold include opioid analgesics (especially meperidine), beta-lactam and quinolone antibiotics, bupropion, theophylline, antipsychotic drugs (especially clozapine and phenothiazines), and isoniazid. Withdrawal from benzodiazepines or barbiturates can precipitate seizures.

Epilepsy

Epilepsy is defined as a condition of recurrent, unprovoked seizures. The incidence of epilepsy rises throughout adulthood. In adults older than 60 years, the annual incidence exceeds 100 per 100,000 population.[3] Begley et al[10] estimated that of the 2.3 million Americans with epilepsy, 24% (549,000) are older than 65 years and 11% live in nursing homes or assisted-living environments. New-onset epilepsy develops in an estimated 60,000 US adults over 65 each year, and 16,000 of them will continue to have seizures despite treatment.[10]

In about 50% of cases of epilepsy in the elderly, no cause is ascertained. For those in whom a cause is determined, the risk for epilepsy is highest in the first year or two after the insult.[3] As it is for acute symptomatic seizures, stroke is the most common cause of epilepsy in the elderly, accounting for 30% to 50% of cases in this age group.[3,11,12] Persons with cerebrovascular disease have a risk of epilepsy more than 20 times that of the general population.[13] The risk for developing seizures after a stroke ranges from 9% to 19%.[14]

Although most epilepsy in the elderly is idiopathic or a result of cerebrovascular disease, other causes have been identified. Degenerative disorders account for 11.7% of cases of epilepsy in the elderly.[3] Among elderly patients with dementia, 9% to 17% will develop epilepsy.[15] Neoplasms are associated with 4.5% to 10%

of cases, and trauma accounts for about 3%.[3,16,17]

PATHOPHYSIOLOGY OF SEIZURES IN THE ELDERLY

The potential mechanisms of epileptogenesis in the elderly are complex and incompletely understood. For example, the accumulation of comorbid conditions may lead to an increased occurrence of epilepsy in the elderly, or common age-related changes in the brain might cause altered neuronal response to insult, resulting in seizures. Various animal models have suggested an age-dependent susceptibility to seizures, but it is unclear whether humans have a similar susceptibility.[18–22]

Numerous changes in brain chemistry, neuronal function, and anatomy occur with human aging. These include neuronal dropout, synaptic loss and reorganization, and histologic abnormalities such as lipofuscin or amyloid deposition. These processes may alter the response of the aging brain to neurologic and systemic insults, thus contributing to the increased risk of epilepsy in the elderly.[23]

CLINICAL FEATURES

Seizures may have partial or generalized onset in the brain. Partial seizures involve a focal area of the brain, and their clinical manifestations vary according to the brain region involved. A partial seizure can spread to become a tonic-clonic seizure (secondary generalization). Generalized seizure types include absence, myoclonic, atonic, tonic, and tonic-clonic. Table 1 summarizes the most common seizure types and their typical clinical features.[24]

Manifestation differs between elderly and young

The manifestations of seizures in the elderly often differ from those in younger patients and may be challenging to diagnose. Vague presenting complaints such as confusion, altered mental status, or memory problems are common in the elderly with new onset of epilepsy. Focal clonic seizures, versive seizures, and bilateral asymmetric tonic seizures occur less frequently in elderly patients than in younger patients.[25]

The lack of typical clinical signs in the elderly may lead to delayed diagnosis and treatment. In the Veterans Affairs Cooperative Study of epilepsy in the elderly (also known as the VA Cooperative Study 428),[11] epilepsy was not considered in 26% of the initial medical evaluations of elderly patients who eventually were diagnosed with epilepsy.[26] Alternative diagnoses were altered mental status (41.8%), confusion (37.5%), blackout spells (29.3%), memory disturbance (17.2%), syncope (16.8%), dizziness (10.3%), and dementia (6.9%) (patients could have more than one initial diagnosis).[26]

Frequently, the symptoms of epilepsy in the elderly are attributed to other comorbid conditions. Postictal Todd's paralysis may be prolonged in the elderly, leading to the misdiagnosis of cerebrovascular disease rather than epilepsy.[27] In elderly patients with a history of transient ischemic attack (TIA) or stroke, the time to diagnosis of epilepsy was 1.7 years.[28]

Complex partial seizures (see Table 1) are the most common seizure type in the elderly, but certain features distinguish them from complex partial seizures in younger adults. While most complex partial seizures in the general population originate in the temporal lobe, in the elderly they are more likely to be extratemporal, usually frontal, coinciding with the areas of the brain that are frequently affected by stroke.[26] The elderly are less likely to experience the types of auras usually associated with temporal lobe epilepsy and instead report nonspecific symptoms, such as dizziness. Automatisms occur less frequently in complex partial seizures in the elderly, and postictal confusion may be prolonged.[26]

Video-electroencephalographic (EEG) monitoring has permitted accurate clinical characterization of paroxysmal events in the elderly. A recent study of video-EEG monitoring results in the elderly found that only about half had epileptic seizures, whereas psychogenic events were the most common type of nonepileptic spell.[29] The surprisingly high percentage of psychogenic events in this series emphasizes the need for definitive diagnosis of spells in the elderly.

DIFFERENTIAL DIAGNOSIS

Seizures must be differentiated from spells due to a variety of other causes, both neurologic and non-neurologic. Other common neurologic causes of such spells in the elderly include syncope, TIA, transient global amnesia, and episodic vertigo.[30] Cardiovascular disorders such as aortic stenosis, congestive heart failure, and arrhythmia can cause spells due to impaired cerebral blood flow. Antihypertensive or diuretic medications, as well as dehydration, can contribute to orthostatic hypotension. Less common causes of spells include migraine, sleep disorders, and psychogenic events. This broad differential diagnosis can be narrowed on the basis of the history, physical examination, and diagnostic tests.

A good history is critical in determining the diagnosis. The history should focus on a description of the event, any specific symptoms that preceded it, its duration, and any previous occurrence of spells. Patients are often unable to recall their spells or may be unaware of them, so it is helpful to interview caregivers for further details. The physician should also inquire about cardiac

TABLE 1
Clinical characteristics of seizure types

I. Partial seizures (seizures with focal onset)

A. Simple partial seizures

Consciousness is not impaired during simple partial seizures. The patient can respond appropriately to questions and commands and can remember events occurring during the seizure. The principal types are:

1. *Motor seizures*, which are characterized by localized stiffening or jerking of the face or extremity on the same side of the body.
2. *Somatosensory or special sensory seizures*, which can include any sensory modality including smell, taste (often unpleasant—eg, a metallic sensation), vision (such as flashing lights), hearing, or touch (such as paresthesias and electrical sensations).
3. *Autonomic seizures*, which are relatively common and may include changes in visceral sensation (eg, in abdomen or chest) and change in heart or breathing rates.
4. *Psychic seizures*, in which patients report feelings of fear, depression, or anxiety, or altered perceptions of time such as déjà vu and jamais vu.

B. Complex partial seizures

Complex partial seizures are characterized by impairment of consciousness. Frequently, the patient has automatisms, characterized by automatic movements such as lip-smacking, picking at bed sheets, grunting, or more complex acts. Complex partial seizures usually last no longer than 3 minutes, with postictal confusion lasting 15 minutes or less. These may begin as simple partial seizures and progress to impairment of consciousness, or there may be impairment of consciousness at the onset.

C. Secondarily generalized seizures

Partial seizures can secondarily generalize. Patients may describe an aura, which is a simple partial seizure preceding the loss of consciousness. Patients may also experience a complex partial seizure before the seizure becomes secondarily generalized.

II. Generalized seizures (seizures without focal onset)—the major types are absence, myoclonic, atonic, tonic, and tonic-clonic

A. Absence seizures

Absence seizures are usually classified as either true or typical absence (previously known as petit mal) or atypical absence.

1. *Typical absence seizures* are characterized by abrupt onset of impairment of awareness and responsiveness lasting 3 to 20 seconds. Return to awareness is immediate after the seizure ends. There is no warning before the seizure and no postictal confusion. The patient may report automatisms such as eye-blinking and lip-smacking. The EEG is important in making a diagnosis in this type of seizure and demonstrates a generalized 3-Hz spike-and-wave discharge.
2. *Atypical absence seizures* are usually seen in children with cognitive impairment as opposed to typical absence. They may be associated with atonic and tonic seizures. The EEG usually shows a generalized, slow, spike-and-wave complex (ie, < 2.5 Hz).

B. Myoclonic seizures

Myoclonic seizures are characterized by very brief bilateral synchronous jerks. Consciousness is usually not impaired unless there are successive myoclonic seizures. EEG generally demonstrates a polyspike-and-slow-wave discharge.

C. Atonic seizures

Atonic seizures are characterized by a sudden loss of postural tone with impairment of consciousness. These seizures rarely last more than 1 minute and generally last less than 5 seconds.

D. Tonic seizures

Tonic seizures are characterized by flexion or extension of both the upper and lower extremities. They generally last from 5 to 20 seconds and are common in patients with other neurologic abnormalities.

E. Tonic-clonic seizures

Primary generalized tonic-clonic seizures are not preceded by an aura and are characterized by an initial tonic phase of stiffening followed by a clonic phase of jerking of the extremities. The seizure lasts about 30 seconds to 2 minutes. It may be difficult to differentiate a primary generalized tonic-clonic seizure from a secondarily generalized seizure.

Adapted from reference 24.

risk factors and symptoms, medications, coexisting medical conditions, head trauma, and alcohol use. Table 2 lists factors to be considered in evaluating the patient who presents with a spell of unknown cause.[30,31]

DIAGNOSTIC EVALUATION

Routine investigations

Acute symptomatic seizures commonly have toxic and metabolic etiologies. Thus, patients who present with one or more acute seizures should be evaluated with a complete blood cell count, liver function tests, urinalysis, and measurement of electrolytes, calcium, and magnesium. Toxicology screening for drugs and alcohol should be considered. If the patient is febrile or immunosuppressed, a lumbar puncture is indicated. Oxygen saturation should be checked, and arterial

blood gases should be measured if respiratory compromise is suspected.

Electroencephalogram

Older patients with acute seizures may have a variety of EEG changes, only some of which are attributable to underlying pathology. EEGs of patients with encephalopathies often demonstrate diffuse slowing of the background activity or more specific waveforms, such as triphasic waves. Focal changes can occur if there is a structural CNS lesion. Although benign EEG variants with epileptiform morphology occur in all age groups, three that occur with a greater frequency in the older population are subclinical rhythmic electrical discharges of adulthood, wicket spikes, and small sharp spikes.[32] These patterns can potentially be misinterpreted as epileptiform abnormalities.

Interictal epileptiform activity occurs less frequently in older than in younger age groups.[33] Thus, elderly patients have a greater likelihood of nondiagnostic findings on a routine EEG. The VA Cooperative Study 428, conducted in elderly subjects, found interictal epileptiform activity in about one third of routine EEGs.[34] Prolonged EEG recording, ambulatory EEG, and inpatient video-EEG monitoring significantly increase the diagnostic yield.[29] Although elderly patients account for approximately 25% of newly diagnosed seizures in a general practice setting, they are relatively underrepresented in epilepsy-monitoring units.[25] Despite its usefulness in establishing a definitive epilepsy diagnosis in the elderly, long-term video-EEG monitoring remains underused.[29,35]

Neuroimaging

Neuroimaging is recommended as part of the initial evaluation of all older patients who present with a first seizure.[36] The underlying pathology, particularly strokes, can be identified in most elderly patients with seizures. The VA Cooperative Study 428 found that only 18% of elderly patients with epilepsy had normal findings on brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]).[26] Abnormal neuroradiology findings included cerebrovascular accidents (in 42.6% of patients), small-vessel disease (40.9%), encephalomalacia (9.1%), benign tumors (1.5%), and normal-pressure hydrocephalus (0.75%).[26] MRI is usually more sensitive than CT in detecting pathologic processes associated with seizures. CT is more widely available in emergency departments, however, and is appropriate when acute hemorrhage is suspected or MRI is contraindicated.

ANTIEPILEPTIC THERAPY

An acute symptomatic seizure with an obvious precipitating cause does not require AED therapy to prevent further seizures. Rectifying the underlying etiology is the appropriate management for such cases.

For older patients with an isolated idiopathic seizure, the question of therapy becomes more complex. Older persons who present with an initial seizure are more likely than younger individuals to have recurrent seizures.[37] The risk factors that are associated with an increased risk for seizure recurrence in younger patients—known symptomatic cause, partial seizures, a family history of epilepsy, epileptiform EEG, and abnormal neurologic findings—may predict seizure recurrence in the elderly as well.[38] At present, there are few studies to guide us in counseling older patients about future risk following an unprovoked seizure. AED therapy should be initiated for patients with epilepsy, and it should be considered for those with an unprovoked seizure and high risk of recurrence.

AED pharmacokinetics and the elderly

The pharmacokinetics of AEDs are more complex in the elderly than in younger patients because of lower protein binding, impaired hepatic metabolism, altered volume of distribution, decreased renal elimination, and decreased enzyme inducibility. Because polypharmacy is more prevalent in the elderly, AED therapy carries a greater risk of adverse effects (Table 3)[39,40] and drug interactions (Table 4) in elderly patients.

The optimal AED for use in this population would be fully absorbed and demonstrate linear pharmacokinetics, with clearance unaffected by renal impairment. It would neither induce nor inhibit hepatic enzymes. It would be inexpensive and well tolerated and would not interact with other medications. Unfortunately, there is no medication that completely fulfills these ideal characteristics.

AED use in the elderly is widespread

AEDs are widely prescribed for the elderly: 7.7% of nursing home residents are receiving AEDs upon admission to a nursing home, and AED therapy is initiated in another 2.7% within the first 3 months of nursing home admission.[41] AEDs account for almost 10% of adverse drug reactions in the elderly and are the fourth leading cause of adverse drug reactions in nursing home residents.[42]

Despite these statistics and the dramatic increase in treatment options for epilepsy over the past decade, few studies have specifically addressed the clinical use of AEDs in the elderly. Recent guidelines from the

TABLE 2
Variables that distinguish common causes of spells in the elderly

Variable	Seizure	Syncope	TIA	TGA	Metabolic	Psychiatric
Premonitory symptoms	None vs aura	None vs N/V, light-headedness, diaphoresis	None	None	None	None
Posture effect	None	Often erect	None	None	None	None
Onset	Acute	Variable	Acute	Acute	Acute	Variable
Bystander observations						
Duration	1–2 minutes	Seconds to minutes	Minutes to hours	Hours	Minutes to hours	Minutes to hours
Movements	Variable tonic-clonic movements	Loss of tone, clonic jerks	Deficits along vascular pattern	None	Variable, myoclonus, tonic-clonic	Variable, may have bizarre signs
Incontinence	Variable	None	None	None	None	None
Heart rate	Increased or decreased	Variable	Normal	Normal	Variable	Variable
EEG during ictus	Epileptiform pattern	Diffuse slowing	Focal slowing or normal	Rare slowing	Diffuse slowing	Normal
Trauma	Tongue laceration or ecchymoses	Ecchymoses or fracture	None	None	Rare	None
Postictal	Confusion, sleep	Alert or mild confusion	Alert	Alert	Alert when treated	Alert

Adapted, with permission, from reference 30.
TIA = transient ischemic attack; TGA = transient global amnesia; N/V = nausea and vomiting; EEG =electroencephalogram

American Academy of Neurology (AAN) and the American Epilepsy Society (AES)[43] address the use of second-generation AEDs to treat new-onset epilepsy in adults and children. These recommendations generally can be extrapolated to older patients, particularly with regard to safety and tolerability.

Older vs newer AEDs

The choice of an appropriate AED is initially dictated by the patient's seizure type. The older and newer generations of AEDs (Table 3) have efficacy for seizures with partial onset, including simple partial, complex partial, and secondarily generalized seizures. Traditionally, the older AEDs have been used as first-line agents, and the eight newer AEDs (all introduced to the US market from 1993 onward) have been used as adjunctive therapy (or, in the case of lamotrigine, conversion to monotherapy). Valproic acid is a broad-spectrum older AED that is effective for absence and myoclonic seizures, as well as seizures of partial onset. It is the first-line treatment for primary generalized tonic-clonic seizures, although newer AEDs such as lamotrigine, topiramate, and zonisamide also may be effective. Non-drug treatment options, such as vagus nerve stimulation and epilepsy surgery, are generally well tolerated by older adults but are reserved for medication-resistant epilepsy.[44–46]

After seizure type, a variety of factors affect the choice of AED, including potential side effects and cost. Older and newer AEDs are both efficacious, but the older drugs have a higher rate of drug-specific adverse effects, drug interactions, and nonlinear kinetics.[26] Phenobarbital and primidone, both old drugs, are not recommended for use in the elderly because of concern about cognitive impairment and other adverse effects. Total phenytoin concentrations in individual nursing home residents can vary two- to threefold, even when the dose is the same, putting this population at risk for seizures or toxicity.[47]

Despite the drawbacks of older AEDs, phenytoin is the AED most commonly prescribed for nursing home residents, and phenobarbital is the second most commonly prescribed adjunctive AED in this setting.[48] A recent retrospective study speaks directly to

TABLE 3
Comparative characteristics of older and newer antiepileptic drugs (AEDs)

Drug	Primary route of elimination	Advantages	Potential adverse effects	Idiosyncratic reactions	Representative maintenance dose	Cost*
Older AEDs						
Carbamazepine	Hepatic	Inexpensive	Ataxia, dizziness, drowsiness, diplopia, nausea	Rash, blood dyscrasia, SJS, hepatic failure, hyponatremia	400 mg twice daily	$15.30
Phenytoin	Hepatic	Inexpensive, once-daily dosing	Ataxia, gingival hyperplasia hirsutism, lymphadenopathy, nystagmus	Rash, hepatotoxicity, SJS, blood dyscrasias, aplastic anemia, neuropathy, lymphadenopathy, pancreatitis	200 mg once daily	$15.00
Valproic acid	Hepatic	Broad spectrum	Tremor, nausea, ataxia, somnolence	Rash, thrombocytopenia, blood dyscrasia, pancreatitis, SJS, hepatotoxicity	250 mg three times a day	$52.50
Phenobarbital	Hepatic	Inexpensive, once-daily dosing	Sedation, drowsiness, cognitive impairment	Hypersensitivity reactions, seizure exacerbation	90 mg once daily	$2.75
Newer AEDs						
Felbamate	Hepatic	Broad spectrum	Anorexia, nausea, weight loss, insomnia	Rash, aplastic anemia, SJS, hepatic failure, weight loss, anorexia, insomnia	400 mg three times daily (after meals)	$176.90
Gabapentin	Renal	No interactions with other AEDs	Somnolence, dizziness, fatigue, peripheral edema	Neutropenia	300 mg three times daily	$132.96
Lamotrigine	Hepatic	Broad spectrum	Rash, tremor, nausea, dizziness, headache	Rash, SJS, blood dyscrasia	150 mg twice daily	$231.00
Levetiracetam	Renal and hepatic	No drug interactions	Somnolence, dizziness, incoordination, agitation, psychosis	None reported	500 mg twice daily	$148.50
Oxcarbazepine	Hepatic	Better tolerated than carbamazepine†	Dizziness, nausea, diplopia, tremor	Rash, hyponatremia	600 mg twice daily	$231.60
Tiagabine	Hepatic	Clearly defined mechanism of action	Dizziness, sedation, confusion	Rash, paresthesias	32 mg/day (in three divided doses)	$231.30
Topiramate	Renal	Broad spectrum, weight loss	Cognitive impairment, dizziness, ataxia, tremor, fatigue, anorexia, weight loss, sedation, paresthesias	Nephrolithiasis, narrow-angle glaucoma	100 mg twice daily	$240.00
Zonisamide	Hepatic and renal	Once-daily dosing, broad spectrum	Somnolence, dizziness, ataxia, agitation,weight loss	Nephrolithiasis, rash, SJS, cross-allergy to sulfonamides, aplastic anemia	100 mg twice daily	$140.00

Adapted from references 39 and 40.

* Cost for 30-day supply with lowest given dosage of solid formulation, based on average wholesale price from *Drug Topics Red Book*, 2005 ed.

† Oxcarbazepine is an analog of carbamazepine.

SJS = Stevens-Johnson syndrome

TABLE 4
Drug-interaction profiles of the older and newer antiepileptic drugs (AEDs)

Drug	Drug interactions
Older AEDs	
Carbamazepine	Levels markedly raised by propoxyphene; decreases levels of calcium channel blockers (diltiazem, verapamil); its own levels are increased when taken with calcium channel blockers
Phenytoin	Carbamazepine and phenobarbital may reduce phenytoin serum levels; phenytoin serum levels may be increased by fluoxetine, H_2-antagonists, and valproate; phenytoin may impair efficacy of corticosteroids, warfarin, calcium channel blockers, oral contraceptives, and tricyclic antidepressants
Valproic acid	Can act as a metabolic inhibitor, increasing levels of lamotrigine, phenobarbital, and lorazepam; concomitant use may increase levels of phenytoin, diazepam, warfarin, amitriptyline; clearance of valproate may be increased with phenytoin, phenobarbital, primidone, and carbamazepine
Phenobarbital	Increased risk of acetaminophen toxicity; decreases levels of calcium channel blockers; decreases effect of warfarin
Newer AEDs	
Felbamate	May increase valproic acid and phenytoin levels; may decrease carbamazepine levels; may increase phenobarbital levels
Gabapentin	Does not reduce or inhibit any CYP-450 or UGT isoenzyme; does not interact with other hepatically metabolized drugs such as AEDs, warfarin, or theophylline; elimination is not impaired by other drugs
Lamotrigine	Metabolism significantly induced by phenytoin, carbamazepine, phenobarbital; metabolism significantly inhibited by valproic acid; no interaction with gabapentin, levetiracetam, topiramate, zonisamide
Levetiracetam	Does not induce or inhibit any CYP-450 or UGT isoenzyme; no known interactions with other AEDs; no effect on digoxin or warfarin
Oxcarbazepine	Inhibits CYP-2C19; induces CYP-450 3A4 and UGT isoenzymes; magnitude of interactions less than that of carbamazepine (of which oxcarbazepine is an analog); may increase phenytoin levels
Tiagabine	Does not induce or inhibit any CYP-450 or UGT isoenzyme
Topiramate	May increase serum phenytoin levels, presumably via inhibition of CYP-2C19; induces CYP-450 3A4 isoenzymes
Zonisamide	Does not inhibit the CYP-450 system; no effect on phenytoin, carbamazepine, valproic acid, or other drugs; half-life is reduced by phenytoin, carbamazepine, and valproic acid; metabolism is induced or inhibited by drugs that induce or inhibit CYP-450 3A4 isoenzymes

UGT = uridine diphosphate-glucuronosyltransferase

the issue of inappropriate AED prescribing for the elderly.[49] This analysis, which collected data from 21,435 elderly veterans with epilepsy, showed that most patients received potentially inappropriate AED therapy; phenytoin was prescribed for approximately 54% and phenobarbital for 17%.

Other recent studies have suggested that tolerability is a major limiting factor in the medical treatment of epilepsy in the elderly, particularly with older AEDs.[26] A multicenter, double-blind trial in elderly patients with newly diagnosed epilepsy showed a significantly greater dropout rate for subjects randomized to the older AED carbamazepine compared with the newer agent lamotrigine.[50] More recently, the VA Cooperative Study 428, an 18-center, parallel, double-blind trial, compared gabapentin, lamotrigine, and carbamazepine in patients aged 60 years or older with new-onset seizures.[11] Although seizure control in the three treatment groups was similar, there were significant differences favoring the newer agents gabapentin and lamotrigine over carbamazepine in measures of tolerability.[11] Using retrospective data, two reports suggest that the newer AED levetiracetam is effective and well tolerated in the elderly,[51,52] but larger, prospective studies are needed to substantiate these findings.

Although a detailed review of clinical trials of the new AEDs is beyond the scope of this article, readers are referred to the 2004 report by LaRoche and Helmers[53] for such a review. After conducting a systematic literature search and analysis of all randomized controlled trials (n = 55) of the eight newer AEDs in adults, these authors reported that no ran-

domized trials at that time had compared the new AEDs with each other or against the older AEDs. They concluded, however, that several studies suggested that the newer agents have a broader spectrum of antiseizure activity than the older AEDs, fewer drug interactions, and better overall tolerability.

Thus, the newer AEDs offer some advantages over the older AEDs, as detailed in Tables 3 and 4. However, the newer AEDs also have their own drawbacks. These include drug-specific side effects, slower titration schedules, and a lack of intravenous formulations. In addition, all the newer AEDs are significantly more expensive than their older-generation counterparts (Table 3). Further clinical trials clearly are needed to assess the efficacy and safety of the newer AEDs as adjunctive treatment and as monotherapy in the elderly.

Dosing in patients with renal or hepatic dysfunction

Renal function plays an important role in the excretion of AEDs. Glomerular filtration and creatinine clearance decrease by about 1% per year after age 40.[16] In elderly patients with renal insufficiency, dose reductions of AEDs with significant renal excretion are necessary to avoid intoxication. Dose adjustments should be made for gabapentin, topiramate, zonisamide, oxcarbazepine, lamotrigine, levetiracetam, phenobarbital, and primidone.[54] In AEDs with high protein binding, such as phenytoin, uremia is associated with decreased binding. In these instances, monitoring of the free (unbound) fraction is appropriate.[54]

Hepatic metabolism also slows with aging. While concentrations of liver enzymes do not change,[16] cytochrome P-450 microsomal concentrations can be altered by disease, concomitant medications, and nutritional disorders. Several categories of liver disease affect drug metabolism and elimination, including acute hepatitis, cholestasis, chronic liver disease, drug-induced hepatotoxicity, and neoplastic disease. In elderly patients with hepatic disease, phenytoin, valproic acid, phenobarbital, carbamazepine, benzodiazepines, lamotrigine, and tiagabine pose a risk for intoxication, requiring dose reduction and monitoring.[54]

Prognosis with AED therapy

The prognosis for elderly patients with epilepsy treated with AEDs is generally good. In the VA Cooperative Study 428, when seizures occurring during the titration phase were excluded, 63% of elderly patients who continued AED treatment were seizure-free at 1 year.[11] In a Canadian study of elderly subjects with new onset of seizures, 89% of the patients available for follow-up were taking AEDs, and seizure control was usually successful. Predictors of persistent seizures were having more than three seizures by the time of presentation, interictal epileptiform activity on EEG, and discontinuation of AEDs because of lack of efficacy.[55]

STATUS EPILEPTICUS IN THE ELDERLY

About 30% of acute seizures in the elderly present as status epilepticus (SE), a neurologic emergency associated with high mortality.[56] The incidence of SE in the elderly, 86 cases annually per 100,000 population, is almost twice that in the general population.[57] A European study of SE found more than a tenfold increase in the incidence of SE in the elderly compared with adults younger than age 60.[58] The "very old" elderly, those older than 80 years, have an SE incidence of 100 per 100,000 population per year.[59] In the general population, about 4 in 1,000 people who live to age 75 will have had an episode of SE.[60]

Etiologies in the elderly

As is the case with epilepsy, SE in the elderly is most often attributable to acute or remote stroke.[59,61–64] Other common causes include low AED level, hypoxia, and metabolic disturbances, as well as alcohol-related causes. Tumor, infection, anoxia, hemorrhage, CNS infection, and trauma each cause 10% or less of SE cases.[59]

Seizure type

The most common seizure type in elderly patients with SE is partial with secondary generalization (45%), followed by partial (29%) and generalized tonic-clonic.[59] Generalized tonic-clonic SE has a very high mortality, 49%, but even SE with partial seizures has a mortality of 30% in the elderly.

Nonconvulsive status epilepticus

Nonconvulsive SE (NCSE) in the elderly is challenging to diagnose. In the outpatient setting, it may present as waxing and waning confusion.[65] This type of NCSE generally responds well to an initial intravenous dose of a benzodiazepine. In hospitalized elderly patients, NCSE should be considered when a decreased level of consciousness is unexplained or prolonged. Suspected NCSE should be evaluated with EEG. NCSE has a worse prognosis in the elderly than in younger patients because of the severity of comorbidities in the elderly, including hospital-acquired infections.[66] NCSE mortality was 52% in a study of 25 critically ill elderly patients, and death was correlated with the number of acute life-threatening medical problems on presentation.[67] In this critically ill cohort, treatment of NCSE with benzodiazepines increased the risk of death, and aggressive anticonvulsant therapy did not improve outcome.

Treatment of status epilepticus

The treatment of SE in the elderly has been reviewed in detail elsewhere.[62] The initial recommended treatment consists of intravenous diazepam or lorazepam. If seizures persist, a loading dose of phenytoin or fosphenytoin is subsequently given. Blood pressure and cardiac rhythm must be monitored continuously during a rapid infusion, and if adverse effects occur, the infusion rate should be slowed. SE that is refractory to these therapies is usually treated with general anesthetic agents, and patients require intubation, mechanical ventilation, and careful hemodynamic monitoring in an intensive care unit. EEG monitoring is also recommended to document that electrographic seizures have stopped.

Mortality is linked to etiology

SE is associated with a 38% mortality in the elderly and with an even higher mortality, 50%, among patients older than 80 years.[57,68] Mortality in this population is related to the etiology of SE. Elderly patients who develop SE de novo during a hospitalization have a poor prognosis, which is usually related to underlying conditions.[69] Relatively favorable survival rates (mortality < 6%) are associated with SE resulting from low AED levels, alcohol withdrawal, and idiopathic etiologies.[59]

SPECIAL CONSIDERATIONS

AEDs and bone health in the elderly

Until recently, the risk of osteopenia and osteoporosis in patients taking AEDs was not widely appreciated.[70] AED-associated abnormalities in bone metabolism include hypocalcemia, hypophosphatemia, decreased levels of active vitamin D metabolites, and hyperparathyroidism.[71] Decreased bone mineral density and higher rates of osteopenia and osteoporosis have been documented by dual-energy x-ray absorptiometry (DXA) in adults taking AEDs.[72–76] AED use is a risk factor for bone fracture.[77] The risk of brittle bones and potential fracture is particularly relevant to the elderly, who may already be vulnerable to falls because of seizures or medical problems that impair gait, such as arthritis or neuropathy.

Most studies of AEDs and bone health involve older AEDs, especially phenytoin, phenobarbital, and primidone. AEDs that induce the hepatic cytochrome P-450 system are associated with altered bone metabolism and decreased bone density.[73,78–80] On the basis of animal and human studies, various mechanisms for these alterations have been proposed.[71] Accumulated evidence suggests that phenytoin, phenobarbital, and primidone present risks to bone health; the situation is less clear for other AEDs. There are conflicting study results regarding the effects on bone health of other older drugs, including valproic acid, an inhibitor of the cytochrome P-450 system, and carbamazepine, an inducer.[71] Although there is hope that newer AEDs are less deleterious to bone health than the older AEDs, few studies have systematically examined this issue.[81,82]

The elderly patient with epilepsy should be monitored for abnormalities in bone mineral density. In elderly men and women who have been taking older AEDs for many years, bone mineral density should be evaluated by DXA. Patients should also be advised to get adequate exposure to sunlight, a source of vitamin D.

Quality of life

Although tolerability is a key factor in AED selection for the elderly, few randomized clinical trials of AEDs have specifically reported on quality-of-life issues in this age group. The AAN-AES guidelines,[43] though not specifically geared toward elderly patients, offer recommendations for the treatment of new-onset epilepsy based on quality-of-life issues such as adverse effects. In general, however, rates of early study withdrawal for patients over age 60 are substantial, and adverse effects are common.[83]

Although adverse effects from AEDs are common at any age, elderly adults experience different adverse effects from those in younger adults. A community-based survey of 669 adults, including 155 elderly men and women, found that unsteadiness, upset stomach, dizziness, and disturbed sleep were reported more often by elderly patients than by younger patients, whereas younger patients reported more sleepiness, aggression, and skin problems.[84] Memory problems were frequent in both groups. Fractures were the only injury that was more common in older than in younger adults, reported by 9.3% of elderly patients. Interestingly, elderly patients with epilepsy diagnosed earlier in life reported more injuries than those whose epilepsy was diagnosed later in life. This study found no evidence of increased psychological dysfunction in elderly patients with epilepsy. However, elderly patients with late-onset epilepsy were more likely to report anxiety and depression and rated their overall quality of life less positively than did those whose epilepsy had been diagnosed at an earlier age.

Other quality-of-life issues have significant impact on the elderly. Loss of a driver's license because of seizures threatens the independence of elderly adults, especially those living alone. Older adults on a fixed income may experience financial hardship in paying for health care expenses. In one US cost analysis, the

average direct medical cost per person in the 6 years after an epilepsy diagnosis was $10,612 for elderly patients vs $6,429 for younger patients.[10] Unlike younger employed individuals, whose health insurance often includes prescription drug coverage, elderly patients often pay out of pocket for their medications, making cost an important factor in AED selection.

CONCLUSIONS

Seizures are common neurologic events in the elderly that may present with nuances unique to this population. Physicians who develop expertise in recognizing these nuances will make more timely diagnoses and be less likely to miss the diagnosis. In treating epilepsy, the choice of AED is usually dictated by seizure type and tolerability and may be complicated by issues of comorbidity or age-associated effects on AED pharmacokinetics. Appropriate adjustments in AED prescribing for the elderly include a lower initial dose, slower titration, and a lower target dose than for younger adults. Seizures and epilepsy have important implications for the independence, safety, and quality of life of elderly persons.

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