Seizures and Epilepsy in the Elderly

A focus on multidisciplinary care.

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Although often thought of as a disease of the young, both the incidence and prevalence of epilepsy increase throughout adulthood.\(^1,2\) Epilepsy in the elderly population requires coordination with primary care physicians as well as specialty care physicians. This is both because seizures in the elderly may be symptoms of other illnesses and also because treatments for seizures and epilepsy may be affected by treatment of comorbid illnesses that are more likely to occur in elderly patients. This article focuses on providing optimal team-based multidisciplinary care for elderly patients with seizures and epilepsy.

Incidence and Etiology

The prevalence of epilepsy in the elderly is estimated as 10.8 in 1,000 with yearly incidence of 2.4 in 1,000.\(^3\) Strikingly, approximately 24% of new-onset epilepsy occurs after age 60.\(^4\)

The underlying etiology of epilepsy is different in the older population, and acquired etiologies are more frequent. Brain tumors, primary or metastatic, may account for 10% to 30% of new cases and should be a strong consideration for new-onset seizures after age 55.\(^5,6\) Cerebrovascular disease is the leading identified cause of new-onset epilepsy in the elderly, accounting for up to half of new cases.\(^5\) Neurodegenerative disorders, particularly Alzheimer’s disease (AD), represent another common etiology, with up to 10% to 20% of people with AD developing epilepsy.\(^7\) Traumatic brain injury and extraparenchymal hemorrhages (eg, subdural or subarachnoid hemorrhages), a frequent sequelae of falls, are also seen. Paraneoplastic and autoimmune causes of epilepsy are being increasingly recognized in previously idiopathic cases, although the prevalence of these in the elderly remains unknown and possibly underrecognized.

Clinical Presentation and Differential Diagnosis

Focal-onset impaired-awareness seizures remain the most common semiology, likely driven by the development of new focal lesions,\(^2\) with new-onset generalized epilepsies rarely seen. Extratemporal lobe epilepsies are more common than in the younger population.\(^1\) The presenting seizure semiologies may be identical to those in the younger population: staring spells, orobuccal, or hand automatisms. However, some studies have suggested an increased frequency of atypical events such as memory lapses, confusional episodes, and altered mental status.\(^8\) In addition, postictal states may be prominent and prolonged in the elderly, particularly those with underlying cerebral dysfunction.\(^9\)

Because more subtle presentations may be seen, special attention should be paid to patients with concurrent dementia, particularly AD, in whom new-onset seizures are often under-recognized. Although patients frequently present with mesial temporal symptoms, such symptoms may also be masqueraded as discrete confusional or wandering episodes, often mistaken as fluctuations or sundowning.

Status epilepticus, defined as a single seizure lasting longer than 5 minutes or a cluster of seizures lasting longer than 30 minutes without return to baseline consciousness, increases in incidence after age 60.\(^10\) While convulsive status epilepticus is rarely missed, nonconvulsive status epilepticus, manifesting as altered mental status, unusual behavior, or unresponsiveness, may be initially unrecognized resulting in treatment delays. Although overall prognosis depends on causative etiology, in the elderly, status epilepticus often lasts longer and is associated with increased morbidity. Depending upon existing comorbidities, the mortality rate for status epilepticus in elderly patients may be as high as 50%.\(^11\)

The differential diagnosis for epilepsy is broad in the elderly and includes syncopal events, metabolic disturbances (eg, hypoglycemia or hyperglycemia), transient ischemic attacks, cardiac events or arrhythmias, sleep disorders including REM-sleep behavior disorder, and psychogenic nonepileptic seizures, among other causes.

Primary care providers, gerontologists, and neurologists should all have a high index of suspicion for seizures in patients with cognitive impairments or behavioral
changes. In patients who are having seizures, the possibility of secondary causes or late-onset epilepsy must be carefully assessed. It is essential that all clinicians caring for elderly patients consider and communicate with one another regarding the need to assess patients for seizures and epilepsy.

**Diagnostic Studies**

The clinical history remains foundational in the diagnosis of epilepsy, although there are special challenges in elderly patients. Often in the setting of superimposed medical or cognitive issues, the patient is unaware of the semiology (or event occurrence) of their seizure at the time of their appointment. As such, it is often necessary to call the patient’s friends, family, or care staff during the appointment to ensure an accurate event description. The interpretation of all subsequent evaluation depends on a high clinical suspicion of epilepsy.

Electroencephalography (EEG) remains a cornerstone for diagnosis, although the diagnostic yield of a routine EEG may be lower in the elderly because definite epileptiform activity is less common, and more nonspecific EEG abnormalities are frequently seen.12 Repeat routine EEGs or prolonged ambulatory studies are often necessary if the initial study is indeterminate. Focal slowing on EEG has been identified as a predictor of finding epileptiform abnormalities on ambulatory EEGs.13 In unclear or challenging cases, inpatient video-EEG monitoring may be necessary for event capture and definitive diagnosis.

Brain imaging is necessary in new-onset epilepsy in the elderly to investigate for both explanatory etiologies, such as stroke or tumor, and potentially reversible causes, such as subdural hematoma. MRI is preferred over CT for its ability to visualize subtle changes or abnormalities within the brain tissue. Electrocardiography or Holter monitors should be considered in appropriate cases as cardiac disease, such as atrioventricular block or ventricular tachycardia, may frequently mimic seizures, particularly events with loss of consciousness. Bloodwork, including complete blood count, basic metabolic panel, and occasionally liver function tests are helpful at excluding mimics as well as in guiding medication selection.

Less frequently, sleep studies may be necessary to distinguish nocturnal seizures from parasomnias and other sleep disorders. Lumbar puncture and evaluation of cerebrospinal fluid are not necessary in routine cases but can play a critical role if there is suspicion for a central nervous system infection or other inflammatory process.

**Treatment and Follow-Up Care**

**Selecting the Drug**

Once a patient with a seizure has been evaluated, the decision to start treatment with an antiepileptic drug (AED) depends on ruling out any provoking factors for the seizure and determining recurrence risk. If the recurrence risk is high, for example, with a cortical lesion on neuroimaging, epileptiform EEG findings, or seizure out of sleep, then treatment is warranted.14 Some experts advocate treatment of unprovoked seizures in this age group due to the high risk of recurrence regardless of the findings of diagnostic tests. In general, new-onset seizures in the elderly are easily controlled with medication, with up to 80% of patients responding to medical therapy. The challenge in this patient population is related to medication tolerance. Several factors that affect AED pharmacokinetics15 should be kept in mind, including:

- Prevalence of hypoalbuminemia, which will affect protein-bound medications such as phenytoin, carbamazepine, and valproic acid
- Reduction in liver mass and blood flow
- Renal clearance changes
- Reduced absorption due to delayed gastric emptying, pH fluctuations, and delayed colonic transit time

Enzyme-inducing medications also pose a particular challenge because these can affect the metabolism of commonly prescribed drugs for elderly patients, including statins, antihypertensives, psychotropic medications, chemotherapeutic agents, antibiotics, transplant medications, warfarin, and others. AEDs can also affect vitamin D levels, leading to osteoporosis, and have been linked to increased serologic and imaging markers of cardiovascular and cerebrovascular risk.16 Many AEDs are also known to have cognitive and behavioral side effects, which may exacerbate or mask cognitive and behavioral symptoms of comorbid diseases.

In phase 3 clinical trials for AED approval, elderly patients are often only a small fraction of the patients studied. Randomized studies focusing on new-onset epilepsy in the elderly have evaluated carbamazepine preparations, lamotrigine, and levetiracetam.17-19 Overall, the efficacy is similar among the drugs, although carbamazepine is least well-tolerated. Data on other AEDs are limited to subset analyses of phase 3 trials, retrospective evaluations at tertiary care centers, and prospective observational studies. Randomized studies have also been performed in unique populations including AD, patients with poststroke seizures, and patients with brain tumors. In patients with AD, lamotrigine, levetiracetam, and phenobarbital have been studied, and phenobarbital had the most adverse cognitive effects.20 In a randomized trial of levetiracetam in poststroke patients with seizures, levetiracetam was as effective as carbamazepine and better tolerated with fewer negative effects on executive function, attention, and daily functioning.21 An unblinded phase 2 study showed equal efficacy and tolerability for pregabalin and levetiracetam in patients with brain tumors and epilepsy.22

Fortunately for the treating physician, there are many AEDs available. Because there are drug interaction concerns with enzyme-inducing AEDs, these should be avoided if pos-
sible. AEDs should be chosen based on the type of epilepsy; evaluation of comorbid conditions including cognitive status, anxiety and mood disorders, psychosis, history of nephrolithiasis, and gait instability; evaluation of the drug-safety profile; rapidity with which a therapeutic dose needs to be achieved; cost; and risk of nonadherence (Table). Once a drug is chosen, it should be titrated slowly given the concerns about tolerability. The lowest therapeutic dose should be targeted first. Drug levels for certain medications can be useful in guiding the titration and confirming adherence.

Referring to an Epileptologist

When a diagnosis is in question or when seizures are resistant to 2 AEDs despite good tolerability, then an evaluation by an epilepsy specialist should be considered. In these cases, more prolonged EEG monitoring in an inpatient epilepsy monitoring unit or ambulatory EEG with video can be helpful. Despite concerns about decline in verbal memory, epilepsy surgery remains a curative option for patients with drug-resistant seizures. Less invasive and selective procedures are now available and carry a lower risk of cognitive decline. Vagal nerve stimulation, deep brain stimulation, and responsive nerve stimulation can also be considered in patients who have persistent refractory seizures and are not candidates for surgery. The epileptologist should also be involved when the treating physician does not have the familiarity or comfort level to use specific drugs, or to decide whether the patient is a candidate for medication weaning. In some cases, a transition is needed from one drug to another. For example, drugs such as phenytoin and phenobarbital can be difficult to wean or switch and carry a risk of withdrawal seizures.

Planning Procedures

In addition to coordinating with the primary care and specialty physicians, neurologists treating elderly patients with epilepsy must also be available to surgical and procedural teams to guide periprocedural seizure management. Communication with the proceduralist and any anesthesiologist is crucial to ensure patient safety. A clear description of the patient’s seizure history including prior semiologies and drug responsiveness or resistance is necessary. A patient who has weekly seizures will likely have a seizure during a prolonged hospital stay, and the team must be prepared for such a scenario. Patients should be allowed and reminded to take their AEDs the night prior to and the day of the procedure and then following the procedure. In the case of a colonoscopy, the prep itself may affect extended-release formulations of medications. Certain medications may not be available on formulary at the hospital, and the patient would have to provide them himself or herself. The team performing the procedure should be encouraged to avoid medications that can lower seizure threshold such as antipsychotics, atropine, bupropion, imipenem, meperidine, or tramadol. Significant periprocedural electrolyte disturbances, a history of alcohol abuse, and sleep deprivation related to the stress and pain of a procedure are some of the factors that can affect the seizure threshold. Seizure precautions such as a padded bed should be implemented, especially if a patient has a history of generalized tonic-clonic seizures.

If the patient is unable to tolerate oral medications, then an intravenous (IV) formulation of the same medication can be used as a substitute. Other strategies include using a

| TABLE. MEDICATION CONSIDERATIONS IN TREATMENT OF ELDERLY PATIENTS WITH SEIZURES |
|-------------------|---------------------|
| DRUGS             | CONCERNS            |
| Carbamazepine     | Drug-drug interactions |
| Eslicarbazepine   |                     |
| Oxcarbazepine     |                     |
| Phenobarbital     |                     |
| Phenytoin         |                     |
| Primidone         |                     |
| Topiramate        |                     |
| Valproic acid     |                     |
| Felbamate         | Renal impairment requires dose adjustment |
| Gabapentin        |                     |
| Lacosamide        |                     |
| Levetiracetam     |                     |
| Pregabalin        |                     |
| Topiramate        |                     |
| Zonisamide        |                     |
| Carbamazepine     | Cognitive side effects |
| Oxcarbazepine     |                     |
| Phenobarbital     |                     |
| Topiramate        |                     |
| Valproic acid     |                     |
| Carbamazepine     | Aplastic anemia, hyponatremia, Stevens-Johnson syndrome |
| Oxcarbazepine     |                     |
| Eslicarbazepine   |                     |
| Lamotrigine       | Stevens-Johnson syndrome |
| Phenobarbital     | Dupuytren contractures |
| Phenytoin         | Cerebellar atrophy, gingival hyperplasia, peripheral neuropathy |
| Topiramate/zonisamide | Nephrolithiasis, secondary angle-closure glaucoma |
| Valproic acid     | Hyperammonemic encephalopathy, hepatotoxicity, pancreatitis |

*aLess common than with carbamazepine/oxcarbazepine.*
short-term course of a benzodiazepine or IV AED, although those 2 strategies each carry their own risks. The neurologist should also provide a plan in case of periprocedural seizures usually involving short-acting IV benzodiazepines as needed. Drug-drug interactions should be kept in mind especially with enzyme-inducing AEDs because they can affect antibiotics, steroids, and pain medications. Finally, following the procedure, medication dosages may need adjusting, as drug metabolism can be affected by the amount of blood loss or any renal or hepatic derangements.

**Team-Based Care**

**Wellness and Quality of Life**

The care of the elderly patient with seizures should not solely focus on seizure control. Patients may already be struggling with another neurologic or other disease and will now have to cope with a new diagnosis, loss of driving privileges, and the addition of more medications to an already complicated regimen. The neurologist should serve as a patient advocate and keep in close communication with the patient’s primary care specialist and other members of the medical care team to ensure that the diagnosis is correct, that seizures are prevented, and that the high morbidity and mortality associated with the disease are addressed (Figure). All members of the care team should together emphasize and empathize with common seizure precautions including avoiding heights, driving, unsupervised bathing or swimming, and use of heavy machinery.

Other safety concerns can arise with the use of AEDs. Gait instability with AEDs, especially sodium-channel blockers, is a common side effect, which partially explains the increased risk of falls for these patients. In addition to having interactions with or affecting metabolism of other drugs, enzyme-inducing AEDs may contribute to poor bone health. Thus, if enzyme-inducing AEDs are used, the neurologist must coordinate with the primary care physician regarding screening for bone health, monitoring cholesterol levels, and medication adherence. Medication adjustments are also needed in the setting of renal failure, hemodialysis, or liver failure. Excessive sedation and worsening cognitive performance are other side effects that can contribute to morbidity and may necessitate lower AED doses.

Medication adherence is also of utmost importance, as missed doses can immediately place the patient at risk. If the patient is unable to administer his or her own medications, then a family member or visiting nurse should be enlisted to help. Further supervision of blood-pressure and glycemic control might also be necessary. As noted above, medications that lower the seizure threshold should also be avoided by medical, surgical, and procedural teams, and the neurologist may need to be consulted when any new medication is added.

**Consideration of Comorbid Conditions**

Another key aspect of the collaboration includes addressing seizure triggers. As patients age, their sensitivity to alcohol increases, which can put them at risk of further seizures. Both the neurologist and primary care physician should screen for alcohol abuse and remain vigilant for laboratory derangements, such as elevated liver function tests or elevated mean corpuscular volume that may suggest it. Sleep hygiene should be evaluated, as sleep deprivation is a common seizure trigger. Disrupted sleep could be due to undiagnosed sleep apnea, and a polysomnogram would aid with the diagnosis. Spells of loss of consciousness could be a presentation of a life-threatening arrhythmia and the care team should make sure that such an etiology is ruled out as a seizure mimic.

Patients with seizures may also have comorbid psychiatric conditions that need a multidisciplinary treatment approach. Immediately following the diagnosis, patients are vulnerable and have an increased risk of suicide. AEDs in and of themselves can also cause psychiatric symptoms or exacerbatate an underlying psychiatric disorder. The neurologist must provide guidance to the primary care physician and the psychiatrist and may be required to switch to an AED with a more favorable psychiatric profile. The psychiatrist will need to consider that many psychiatric drugs, including antipsychotics, bupropion, clozapine, and lithium lower the seizure threshold.

**Conclusion**

Although usually successful, the treatment of seizures in the elderly requires a coordinated effort. All care providers for these patients must work together to ensure medication tolerability, avoidance of drug interactions, seizure triggers including drugs that lower the seizure threshold, comorbidities that may be masked or worsened by seizures and epilepsy, and patient safety and quality of life. (Continued on page 52)


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