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EPILEPSY BOARD REVIEW MANUAL

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Statement of Editorial Purpose

The Epilepsy Board Review Manual is a study guide for trainees and practicing physicians preparing for board examinations in epilepsy. Each manual reviews a topic essential to the current management of patients with epilepsy.

NOTE FROM THE PUBLISHER:

This publication has been developed without involvement of or review by the American Board of Psychiatry and Neurology.

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INTRODUCTION

Many clinical conditions can result in acute symptomatic seizures. These provoked seizures can arise from metabolic and electrolyte imbalances or from structural central nervous system insults such as infection, tumor, or stroke. Unprovoked seizures, on the other hand, are produced by a different pathology and predispose to recurrence of seizures. Epilepsy has been defined by an enduring predisposition to generate 2 unprovoked seizures that are at least 24 hours apart.

Epilepsy is a common neurological disorder, with a lifetime prevalence of 3.5 to 10.7 cases per 1000 person-years. The prevalence of epilepsy increases progressively after age 60 years. A study conducted in Rochester, Minnesota, showed that the annual incidence of epilepsy increased from approximately 28 per 100,000 population per year at age 50 years to 40 per 100,000 population per year at age 60 and 139 per 100,000 population per year at age 75 years. The increasing incidence of epilepsy with advancing age was also seen in a recent study from rural Iceland, a more homogenous Caucasian population, where an epidemiological survey was supplemented by review of referrals to electroencephalographic facilities and neurologic specialists to identify all individuals with unprovoked seizures or receiving treatment for epilepsy. The frequency of status epilepticus is higher in patients over the age of 60 (32%, 180/546) as compared with younger adults (10%, 60/546). The mortality from status epilepticus in elderly patients (30%) is also higher than that in younger adults (15%). Mortality from status epilepticus rises sharply in older elderly patients, reaching nearly 50% in those aged 80 years and older.

Epilepsy in the elderly is unique and has specific aspects that are not applicable to younger individuals. The etiologies, clinical manifestations, and findings on electroencephalography (EEG) in elderly patients may be different from those in younger individuals, and the treatment of epilepsy in this age-group requires special attention to the pharmacokinetic changes that are seen with increasing age. Elderly patients with epilepsy are often on polytherapy because of different comorbidities, which can result in pharmacokinetic and pharmacodynamic interactions affecting the efficacy of therapy and quality of life of these patients.
As patients with epilepsy grow older, seizures may persist. Increasing age changes the phenotypic manifestation of some seizures; for example, in a study of partial epilepsy of long duration, seizures became briefer with fewer clinical features in association with aging.9 Secondarily generalized tonic-clonic seizures remitted in approximately 84% of patients with increasing age.9 Some seizure types can disappear with age (eg, childhood absence epilepsy, juvenile myoclonic epilepsy) in a small fragment of patients.10 However, absence seizures can persist well into old age. There are case reports of reemergence of seizures in old age in patients with idiopathic generalized epilepsy who have been seizure-free for a long time.11 Reemergence of seizures may become a problem for elderly patients, especially when benzodiazepines are abruptly stopped during elderly patients' hospitalization.

This article focuses primarily on diagnosis and management of de novo epilepsy in older patients.

**SEMIOLGY**

In the majority of elderly patients with epilepsy, epilepsy is predominantly partial epilepsy. The different partial seizure semiology seen in younger adults can be seen in elderly patients (ie, simple partial seizures, complex partial seizures, and secondarily generalized tonic-clonic seizures).12 In elderly patients with epilepsy, most seizures are complex partial seizures (43%–49%).12-14 A video EEG study analyzing the seizure semiology in elderly patients showed no major differences in the frequency of seizure types between elderly patients and a younger control group matched according to location of the epileptogenic focus.15 However, others suggest that elderly patients may have atypical presentations, mostly extratemporal onset, such as altered mental status, memory lapses, and episodic confusion, and that auras are less common. These atypical semiologic features often pose a diagnostic dilemma and result in delayed recognition of the diagnosis.16 Postictal confusion tends to be longer in elderly patients compared to younger adults, and may last for hours, days, or even 1 to 2 weeks.17 This prolonged postictal state may appear as delirium and mimic dementia, further complicating a diagnosis of epilepsy.

Generalized-onset seizures or epilepsy rarely start in the elderly. There are reports of de novo absence status in the elderly, but this condition is likely symptomatic, often related to benzodiazepine withdrawal, and does not necessarily require long-term antiepileptic medications.18

**ETIOLOGY**

The etiology and risk factors for epilepsy in the elderly may be different from those in younger adults. Often brain tumors are considered the foremost risk factor for development of epilepsy in elderly persons, but in clinical practice the risk is overrated. Cerebrovascular disease is the etiology in approximately one-third of elderly patients, and degenerative diseases account for 11.5% of new-onset epilepsy in this age-group.14 Tumors accounted for only 2.7%.14 In a prospective study of 269 patients with stroke who were followed for approximately 6 years, 35 patients (13%) developed seizures.19 In another prospective multicenter study of patients with stroke, approximately 9% developed seizures.20 Patients with hemorrhagic stroke had a greater risk for developing seizures (hazard ratio 1.85; 95% confidence interval [CI] 1.26–2.73; \( P = 0.002 \)) compared with patients with ischemic stroke. Those with disabling cortical infarct or cortical hemorrhage were more likely to develop...
seizures after stroke. Late-onset seizures predisposed patients to developing recurrent seizures (2.3% in this study). In another study, 32% of patients with early poststroke seizures developed late seizures over a mean follow-up period of 26 months, and time to late seizures was shorter in patients with early seizures.

Degenerative neurological disorders such as dementia have been associated with epilepsy in the elderly. In Alzheimer’s disease, seizures are seen in 10% of cases. In a study of autopsy-proven Alzheimer’s disease, 8 patients out of 81 had seizures. Seizures may occur in any stage of the disease in patients with dementia. In a retrospective study of patients with dementia and epilepsy, the most common seizure type was complex partial seizures. In treating patients with dementia and epilepsy, it is important to keep in mind that acetylcholinesterase inhibitors may worsen seizures as well.

Another risk factor for epilepsy in elderly patients is major depression, although major depression can be a consequence of epilepsy as well and is a common comorbidity of epilepsy. Depression has been established as a risk factor for epilepsy in general. Major depression has been associated with a 6-fold increased risk for unprovoked seizures (95% CI 1.56–22) in elderly patients. Major depression alone was associated with an increased risk for unprovoked seizures, in the absence of any known prior neurological insult.

Hypertension is another independent risk factor for new-onset unprovoked seizures. In a case-control study of 227 patients (mean age, 48.1 years) admitted for a first unprovoked seizure and 294 acute surgical controls, history of hypertension was significantly associated with unprovoked seizures, even after adjustment for antecedent stroke and other potential confounders (adjusted odds ratio 1.57). There is a synergism between history of stroke and history of hypertension. These findings were confirmed in another population-based case-control study, in which severe and uncontrolled hypertension increased the risk of epilepsy in patients aged 55 years or older. In this study, diuretics seemed to have a protective effect. This study suggests that treating hypertension aggressively in elderly patients may help prevent worsening of seizures.

The presence of sleep apnea can be a risk factor for developing de novo seizures or worsening of seizures in older patients. In a study comparing the polysomnograms of patients with new-onset or worsening seizures to those patients with epilepsy who were stable or seizure-free, a significantly higher apnea-hypopnea index was noted in patients with new-onset or worsening seizures, suggesting a causative role.

Other risk factors for developing epilepsy present in younger individuals are also applicable in the elderly. Military or civilian head trauma can also be a risk factor in elderly patients, though less frequently than in younger adults.

**DIFFERENTIAL DIAGNOSIS**

Elderly patients are at greater risk for a variety of conditions that can be associated with paroxysmal alterations of behavior or consciousness and can mimic seizures. The differential diagnosis of seizures and epilepsy in the elderly may be different from that in younger adults. The most common conditions in the differential diagnosis of seizures in the elderly are syncope, transient ischemic attacks, transient global amnesia, REM behavior disorder, and nonepileptic psychogenic spells.

Syncope is a common differential diagnosis in elderly patients as syncope can be associated with brief multifocal myoclonus that could be mis-
taken for the motor activity in convulsive seizures. However, tonic-clonic activity in epileptic seizures is preceded by generalized stiffening and is usually bisynchronous. Tonic-clonic seizure is also of longer duration, usually lasting more than 30 seconds, while the multifocal myoclonus of syncope is generally shorter than 20 seconds, with no significant postictal confusion. Tongue biting and urinary incontinence are uncommon in syncope, but are commonly seen with generalized tonic-clonic seizures. On the other hand, palpitations, dyspnea, tunnel vision, pallor, and sweating are commonly seen with syncope, while these features are uncommon in generalized tonic-clonic seizures.

Transient ischemic attacks (TIAs) may mimic seizures in clinical appearance. However, TIAs tend to have a longer duration than seizures. TIAs follow a vascular distribution and manifest with negative symptoms (loss of function, as in weakness and numbness), while seizures are more likely to have positive symptomatology (such as stiffening/jerking and paresthesia). Confusion, which is common with seizures, is usually not seen with TIAs.

Transient global amnesia (TGA) is also in the differential diagnosis of epilepsy in elderly patients. TGA episodes are usually isolated events, characterized by the abrupt onset of anterograde amnesia, with no other neurological deficits. After recovery of short-term memory, the patient remains amnesic for the episode. TGA attacks usually last 1 to 9 hours, while complex partial seizures most often last less than 3 minutes.

REM behavior disorder can mimic seizures in elderly patients. It is characterized by loss of the natural atonia during REM sleep, which results in acting out a dream. Patients usually have a vivid recall of the actual dreams that correlate to the witnessed behavior, while nocturnal complex partial seizures are associated with amnesia for the events. REM behavior disorder manifests more commonly in the latter half of the night when REM sleep dominates, while seizures are more likely to occur in the transition from waking to sleep.

Psychogenic nonepileptic events can be seen in the elderly but should be considered a diagnosis of exclusion because they are not as common in the elderly as in younger adults. In one study with video-EEG monitoring in 23 elderly patients with nonepileptic events, the events were psychogenic in 13 patients (57%).

EVALUATION

In establishing the diagnosis of epilepsy in elderly patients, a detailed history, including eye witness accounts, is as crucial as it is in younger patients. Clinicians treating elderly patients should have a high index of suspicion for epilepsy because elderly patients with new-onset epilepsy are often referred for altered mental status, episodes of confusion, dementia, memory lapses, or syncope.

EEG is the most sensitive and specific test to support the diagnosis of epilepsy. However, its yield in the elderly is lower than that in younger adults. If the first EEG is negative, repeat routine or prolonged EEG recordings may be helpful. However, treatment may be initiated even without EEG evidence of epilepsy, if the history is strongly suggestive of the diagnosis because the risk of seizure recurrence is higher in elderly patients. Magnetic resonance imaging (MRI) is often necessary in elderly patients suspected to have seizures to rule out stroke and tumors. Other studies such as blood tests and lumbar puncture to investigate the etiology of seizures/epilepsy should be considered on an individual basis.

If seizures continue despite treatment, then special testing may be needed to confirm the di-
agnosis and to rule out other conditions in the differential diagnosis. Inpatient video-EEG monitoring in conjunction with antiepileptic drug withdrawal allows the direct recording of events in question and is an important tool to confirm the diagnosis of epilepsy.\textsuperscript{15,38} Alternatively, patients’ caregivers can be advised to capture spells on home video (eg, cell phone) to review the semiology of the spells.

**TREATMENT**

**ANTIEPILEPTIC DRUG THERAPY**

Once the diagnosis of an unprovoked seizure in an elderly patient is made, the question of starting therapy with an antiepileptic drug (AED) is entertained. Clinicians treating elderly patients should have a low threshold for starting AEDs because the risk of recurrence is considerably higher in the elderly, up to 80\%, compared to younger adults.\textsuperscript{16} Due to this high risk of recurrence, elderly patients should be started on antiepileptic medications even after the first unprovoked seizure.

**Selection of an AED**

Clinicians should consider several important issues in selecting the appropriate AED and dosage for each elderly individual with epilepsy. These include age-related changes in pharmacokinetic factors, routes of administration, drug interactions, adverse-effect profiles, and cost of available agents. There are physiological changes in aging that affect medication pharmacokinetics and result in a predisposition to side effects. There may be progressive reduction in creatinine clearance with increasing age as well as reduced hepatic clearance. As a result of these changes, elderly patients may have higher serum concentrations of AEDs compared to younger adults. Moreover, serum albumin levels are low and protein-binding of antiepileptic drugs may be reduced in elderly patients.\textsuperscript{39} This results in a higher protein-free fraction (active fraction) for drugs that are highly protein-bound such as phenytoin and valproate.

Many elderly patients have other comorbidities and are on a variety of medications (eg, antihypertensives, anticoagulants, antiarrhythmic agents, lipid-lowering medications, diuretics, and psychoactive medications). These medications can be affected by AEDs and interaction can be bidirectional. Concurrent administration of AEDs with other medications may result in interactions due to drug effect on hepatic enzymes or due to competition for protein binding, and these interactions can result in clinical symptoms. Similarly, enzyme-inducing AEDs can induce the metabolism of other concomitant medications; for example, carbamazepine and phenytoin can lower the serum concentration of simvastatin.\textsuperscript{40} Phenytoin can also compete with warfarin for protein-binding and can displace warfarin, raising the concentration of free warfarin in the serum.\textsuperscript{41} Enzyme-inhibiting medications such as fluoxetine can increase carbamazepine levels.\textsuperscript{42} Elderly patients often take herbal supplements, adding to the potential for interactions.\textsuperscript{43}

Elderly patients often have poor bone health and are at increased risk for osteopenia and osteoporosis, which may lead to pathological fractures. Enzyme-inducing AEDs are expected to reduce vitamin D levels and increase bone turnover.\textsuperscript{44} However, long-term treatment with AEDs leads to reduced bone mineral density, irrespective of enzyme-inducing capabilities. In one study, the risk of hip fractures was increased by the use of AEDs, especially in women (odds ratio 4.15).\textsuperscript{45} Some experts recommend monitoring vitamin D levels to assess bone health and supplementation with vitamin D/calcium.
Clinical trials with AEDs in elderly patients with epilepsy may provide guidance in choosing the appropriate medications. However, there are relatively few AED trials in elderly patients with epilepsy. Older AEDs have the potential for drug interactions due to their pharmacokinetic properties, and these medications should be avoided in elderly patients. Since 1993 8 new antiepileptic medications have been marketed in the United States. Lamotrigine was the first to be studied in an elderly patient group. Brodie et al compared lamotrigine and carbamazepine in a multicenter, double-blind trial of 150 elderly patients with newly diagnosed epilepsy. Efficacy measures were similar for the 2 drugs, but lamotrigine was much better tolerated compared with carbamazepine. In another international, multicenter randomized double-blind controlled trial of lamotrigine versus sustained-release carbamazepine, no statistically significant differences were seen, but there was a trend for better tolerability with lamotrigine. In sum, lamotrigine is a better choice than carbamazepine in elderly patients with epilepsy.

The first VA Cooperative Study compared carbamazepine, phenobarbital, phenytoin, and primidone in 622 adult patients with partial epilepsy, but they were not specifically elderly patients. Overall treatment success was highest with carbamazepine or phenytoin, intermediate with phenobarbital, and lowest with primidone (P < 0.002). In a second VA Cooperative trial, lamotrigine and gabapentin were compared to carbamazepine in a multicenter, randomized, double-blind, double-dummy, parallel study of 593 elderly patients with newly diagnosed epilepsy. The primary outcome measure was retention in the trial for 12 months. Early terminations occurred more often in the carbamazepine group, mostly due to adverse events (P = 0.0002). However, there were no significant differences in seizure-free rate at 12 months. Based on these results, the study concluded that lamotrigine and gabapentin should be considered as initial therapy for older patients with newly diagnosed seizures. Lamotrigine was better than both carbamazepine and gabapentin in a large unblinded, randomized controlled trial in partial epilepsy that was not specific for elderly patients. That trial also showed that for time to treatment failure, lamotrigine was superior to topiramate and had a nonsignificant advantage over oxcarbazepine. Other drugs were studied in the elderly in a less rigorous manner. Among the old AEDs, phenobarbital and primidone were no longer considered appropriate as first-line treatments due to their poor tolerability in the first large VA Cooperative trial.

Phenytoin and carbamazepine are strong enzyme inducers with potential for adverse interactions. The nonlinear kinetics of phenytoin may become more problematic in the elderly. The phenytoin dose curve was much steeper in the elderly compared to younger adults, and there was considerable variability in phenytoin concentrations in elderly nursing home residents. Phenytoin protein-binding may decrease with age. When only total AED serum levels are considered in dose adjustments, continued titration can potentially lead to toxicity at apparently “therapeutic” total AED levels. Valproate has the advantage of not being an enzyme inducer. However, the second VA Cooperative trial found it to be less effective and less well tolerated than carbamazepine for partial seizures. Valproate is also highly protein-bound, which can be problematic in elderly patients with epilepsy. The kinetics of a single oral dose of sodium valproate were studied in 6 healthy elderly patients and compared with 6 young control subjects. The total plasma valproic acid concentrations were very similar in the elderly and in the young,
but free valproic acid concentrations were significantly increased in the elderly. Chronic valproate treatment has been associated with reversible parkinsonism and cognitive impairment in elderly patients. However, the cognitive adverse effects of valproate were not replicated in a prospective study of 38 elderly patients randomized to valproate or phenytoin. Changes in cognitive function were minor. There was little difference between phenytoin and valproate with regard to impact on cognitive function.

The experience with oxcarbazepine in the elderly population is limited. In addition, oxcarbazepine has been associated with hyponatremia in older individuals, particularly if administered with diuretics. However, hyponatremia was only seen in 3 of 52 elderly patients enrolled in oxcarbazepine clinical trials. This suggested that hyponatremia may be less likely in otherwise healthy elderly patients and may respond well to fluid restriction.

Gabapentin and lamotrigine are both approved for initial monotherapy in the European Union, and a panel of the American Academy of Neurology suggested that both gabapentin and lamotrigine are effective and can be used as first-line treatment of partial epilepsy. Topiramate has Food and Drug Administration (FDA) approval as first-line monotherapy in epilepsy. However, it has an unfavorable cognitive profile in comparison with lamotrigine.

Topiramate can have significant cognitive effects. In a study of 16 consecutive patients (not specifically elderly patients) tested before and after topiramate therapy, 94% of patients showed a clinically significant decline on at least one neuropsychological measure, while only 63% were aware of cognitive side effects. Two studies were performed with topiramate specifically in the elderly. In a double-blind trial of topiramate, elderly patients were randomly assigned to 50 mg/day or 200 mg/day. Efficacy was similar with the 2 dosages when topiramate was used as monotherapy, but 200 mg topiramate was more effective. Only 13% of patients reported a cognitive-related adverse event; other common adverse events were somnolence, dizziness, and headache. Another open label trial that evaluated topiramate in elderly patients with new-onset epilepsy titrated patients to 100 mg/day, with subsequent adjustments as needed clinically. Patient retention was 79% at 7 months, and only 14% dropped out because of poor tolerability. Seizure freedom was reported in 64%, and 87% had an at least 50% reduction in seizure frequency. These trials suggested that low-dose topiramate could be a consideration in the elderly.

Levetiracetam is a broad-spectrum antiepileptic medication with no interactions and with a relatively favorable side effect profile. It was approved in the European Union as initial monotherapy for partial epilepsy after a large comparative trial showed equal efficacy and tolerability to sustained-release carbamazepine. One retrospective study reported favorable efficacy and tolerability of levetiracetam in a small group of elderly patients who were either started on or converted to levetiracetam monotherapy. Levetiracetam was also evaluated as initial monotherapy in 2 studies of elderly patients with late-onset poststroke epilepsy. In one study, seizure-freedom was observed in 82.4% of 34 patients at daily doses of 1000 to 2000 mg. Only 7 patients reported side effects and only 1 discontinued treatment due to adverse effects (somnolence). In the other study, 89.5% of 25 patients were seizure-free. Side effects were reported in 28%, but they were mild and did not result in withdrawal from the study. Levetiracetam was also studied as adjunctive therapy in a subset of 78 elderly patients who participated in a large open-label, community-based trial. Overall, 40%
of patients became seizure-free and 76.9% had a 50% or greater reduction in seizures. Adverse effects, mainly somnolence and dizziness, led to discontinuation in 19.2% of patients. In general, levetiracetam was well tolerated otherwise.69

There are limited data on the use of tiagabine, zonisamide, pregabalin, lacosamide, and eptigabine in the elderly. None of these AEDs have an indication for first-line therapy.

Starting antiepileptic medication in elderly patients requires consideration of seizure type, seizure frequency and severity, comorbid conditions, and concomitant medication. It is generally preferable to start with an AED that is not enzyme inducing, not highly protein bound, and unlikely to interact with other drugs. As a result, the newer AEDs are preferable. Elderly patients are more susceptible to side effects of AEDs and should be started on low doses. Fortunately, the elderly are more likely to respond to lower AED doses and plasma concentrations than younger individuals.16 Since the vast majority of patients with new-onset seizures in old age have partial epilepsy, lamotrigine and gabapentin should be considered first-line agents, based on the most recent VA Cooperative trial.13 Levetiracetam is also a reasonable first choice. Oxcarbazepine may also be considered, but with caution because of the risk for hyponatremia. Topiramate can be used at a low dose, with caution for cognitive side effects, if indicated by comorbidity.

If the first-line AED is effective but not tolerated, then an alternative monotherapy should be tried. If the first AED is not effective at the maximum tolerated dose, either alternative monotherapy or adjunctive therapy is an option.70 Replacement monotherapy is preferable when the first AED was totally ineffective. On the other hand, adjunctive therapy may be more appropriate when the first AED was efficacious but did not lead to seizure freedom. When dual therapy is used in elderly patients, it is important to choose a combination without unfavorable interactions.

AED Withdrawal

If seizures are controlled, AED withdrawal can be considered after at least 2 years of seizure freedom. The decision should be individualized. Criteria to help with this decision are derived from studies in the general epilepsy population, as there are no specific studies in the elderly addressing risk of seizure recurrence after AED withdrawal.

SURGICAL TREATMENT

Medically intractable epilepsy in elderly patients could be considered for surgical treatment, particularly if the epilepsy is related to a focal structural lesion. The presurgical evaluation of elderly patients is similar to that of younger patients, with video EEG, MRI, as well as functional imaging with positron emission tomography in the absence of an epileptogenic lesion on MRI. There are limited data on resective epilepsy surgery in the elderly. Temporal lobe epilepsy surgery was found to be effective for older individuals, though with a slightly higher morbidity than for younger patients. However, most patients who had epilepsy surgery in old age had epilepsy starting earlier in life.71–75

VAGUS NERVE STIMULATION

Vagus nerve stimulation (VNS) has not been widely tested in the elderly. One study evaluated VNS in 45 refractory epilepsy patients aged 50 years or older. A greater than 50% decrease in seizure frequency was noted in 12 patients at 3 months, and in 21 of 31 (67%) patients at 1 year.76 Side effects were mild and transient, with significant improvement in quality of life scores over time.76 However, there are reports that VNS can
worsen sleep apnea, a common comorbidity in elderly patients. Hence, VNS should be used with caution in these patients.

**SUMMARY**

Epilepsy is a common neurological disorder in the elderly, and its incidence is higher in elderly patients. Besides the high incidence, the presentation of seizures may be more subtle in elderly patients compared to that in younger adults. This difference in semiology of seizures may pose a diagnostic challenge at times. Elderly patients may have multiple medical problems and may be on multiple medications that can result in interactions between AEDs, and these medications can result in pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic changes occur with advancing age and this may result in side effects in the elderly patients. Thus, choice of AEDs in the elderly must take into consideration comorbidities, concomitant medications, and age-related pharmacokinetic changes. Seizures in the elderly usually tend to respond better to antiepileptic drugs, and monotherapy can be effective in elderly patients. In elderly patients, treatment should be started with a second-generation AED monotherapy at a low dose and slowly titrated. The newer antiepileptic medications lamotrigine, gabapentin, and levetiracetam are recommended as first-line therapy in the elderly. The key to minimizing side effects is to start at a low dose and titrate gradually up to an effective dose. Epilepsy surgery can occasionally be considered in selected refractory elderly patients.

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