METHODS

This expert panel of interdisciplinary thought leaders representing academia and the medical community was assembled by the Johns Hopkins University School of Medicine Office of Continuing Medical Education to review the existing literature and author this publication on advances in the clinical management of epilepsy in senior patients. Where evidence existed, it served as the basis for specific recommendations. In the absence of evidence, consensus was obtained.

ABSTRACT

Demographic data indicate that new-onset epilepsy is more prevalent in the elderly than in any other age group. Because unprovoked seizures in this age group are frequently due to symptomatic causes (most commonly cerebrovascular), treatment is typically lifelong; therefore, the selection of an appropriate antiepileptic drug (AED) is of critical importance for this patient cohort. First- and second-generation AEDs are available as potential therapy and offer physicians several options. Nonetheless, there is a paucity of rigorous data comparing the efficacy of these agents, and few well-controlled trials examine their use in the elderly population. One recently published landmark study that was begun in the 1990s, the Veterans Affairs Cooperative Study 428, objectively examined treatment issues in an elderly cohort with new-onset epilepsy. Results from this study indicate that successful treatment must take into account tolerability and efficacy. Evidence suggests that select second-generation agents may offer distinct advantages over first-generation agents in elderly patients with epilepsy. In light of these clinical trial results and the specific needs of this patient group, there is a need to revisit treatment practices in the elderly cohort. The treatment parameters of first- and second-generation AEDs in the elderly are evaluated for pharmacokinetics, drug interactions, cognitive profiles, and safety profiles. Selection of certain new AEDs as early therapy in elderly patients with epilepsy can now be strongly advocated, but implementation of these practices requires further educational initiatives targeted to physicians who initially treat these patients.

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INTRODUCTION

The incidence of new-onset epilepsy (recurrent, unprovoked seizures) is greater in the elderly than in any other age group (Figure 1); between the ages of 60 and 85 years, the incidence triples. In 2000, the number of people older than 65 years of age was almost 13% in the United States; this is estimated to increase to 20% by 2030. On admission to long-term care (LTC) facilities, 5.8% of patients have a diagnosis of epilepsy and, within 3 months, an additional 1.5% are given this diagnosis. A total of 10% of LTC residents receive antiepileptic drugs (AEDs), although it is sometimes for indications other than epilepsy.

As the population ages, there is greater recognition of the fact that all patients older than 60 or 65 years cannot be grouped together. The active 65-year-old football coach is, in many ways, different from the disabled 85-year-old living in an LTC facility. However, despite these differences, several of the considerations for therapy are similar. For example, minimizing side effects (especially cognitive effects) and avoiding potential drug interactions are important considerations for all senior patients.

Although the demographic figures underscore the prevalence of epilepsy in the elderly, it is also an appropriate time to re-examine the treatment of epilepsy in this cohort for several other reasons. Since 1993, 9 new AEDs have been approved in the United States.

Felbamate, because of safety concerns, is appropriately reserved for carefully selected patients and will not be discussed further.

Many of the second-generation AEDs offer potential benefits (eg, pharmacokinetic and side-effect profiles) for use in the treatment of epilepsy in the elderly. The recent publication of the landmark Veterans Affairs (VA) Cooperative Study 428 on new-onset epilepsy in the elderly has objectively examined treatment issues and has provided vital information on the characteristics of this important population. Although the trial was begun in the late 1990s, before the introduction of some of the newer second-generation agents, the results are still salient. In this study, efficacy in the treatment of seizures did not differ among the AEDs used, but tolerability of the 2 second-generation AEDs (gabapentin and lamotrigine) was significantly better than carbamazepine. Therefore, successful treatment of the senior patient with epilepsy needs to consider tolerability and efficacy as significant factors. It is in the areas of tolerability and side effects that several of the second-generation AEDs may have definite advantages over first-generation agents. There are few efficacy trials between second-generation and first-generation AEDs and no thorough comparative trials in efficacy among second-generation AEDs (some are under way or being designed). The completed trials were in new-onset epilepsy and did not demonstrate any significant differences in efficacy.

DIAGNOSIS, EVALUATION, AND SEIZURE CLASSIFICATION

Elderly patients with seizures include those patients with long-standing seizure disorders and those with new-onset seizures. When evaluating new-onset seizures, it is important to address potential provocative causes (eg, cardiac, metabolic, and medications) because if these are identified and addressed, long-term AED therapy is not warranted. The elderly patient with an established diagnosis of epilepsy may...
have a variety of seizure types or epileptic syndromes, idiopathic and symptomatic. For example, juvenile myoclonic epilepsy is an idiopathic epileptic syndrome that, although often readily controlled, typically requires lifelong therapy. Complex partial seizures that begin in early adulthood are controlled in only approximately 25% to 50% of patients; many of these patients also require long-term therapy. However, most elderly patients are those with new-onset seizures.

Evaluation of the presentation of new-onset unprovoked seizures in the elderly should focus on seizure classification and etiology. Epilepsy syndromes, significant in young populations, are not as much of a factor in evaluation and selection of treatment in the elderly for new-onset seizures. New-onset seizures in the elderly are usually localization-related (partial), symptomatic (a cause can be identified), or cryptogenic (a cause is suspected but not identified). As a result, the evaluation of new-onset seizures should include magnetic resonance imaging (MRI) because even a computed tomography scan that appears normal may miss many small ischemic events and abnormalities in the temporal lobe regions. In the recent VA Cooperative Study 428, the most commonly identified causes for new-onset seizures in the elderly were cerebral infarction (29.9%), atherosclerosis (15.7%), and head trauma (7.1%). Brain tumors are another potential symptomatic cause of seizures (meningiomas are some of the most common tumors in this age group). Also, Alzheimer’s disease is another common cause of seizures in the elderly; approximately 10% to 20% of patients with Alzheimer’s dementia have at least 1 seizure, and the incidence increases with the severity of the dementia.1,10 However, even with current MRI imaging, 25% of patients may not have an identified cause; these are the patients who are classified as cryptogenic.

An electroencephalogram (EEG) should be obtained as part of the initial evaluation of new-onset seizures; however, it should be recognized that approximately 30% of patients with known seizure disorders have unremarkable interictal EEGs.11 Longer recording times or additional EEGs increase the number of positive tests. The elderly patient also may have frontotemporal sharp forms that are of relatively low epileptogenicity and increased frontotemporal slow activity.8 Dementia and cerebrovascular events, in addition to other symptomatic causes, may provoke EEG changes that are not epileptogenic but may confound the diagnosis. There is little purpose in performing repeat EEGs in elderly patients with a known seizure disorder because most of these patients are not candidates for AED withdrawal.12

Most new-onset seizures in the elderly are symptomatic; therefore, partial seizures with or without secondary generalization are the most commonly identified seizure type. Complex partial seizures composed the most common seizure type in the VA Cooperative Study 428 (251 of 581 patients); generalized tonic-clonic seizures (GTCS), simple partial seizures, mixed partial seizures, and generalized seizures were the other identified seizure types.5 If seizures have a symptomatic (identified or presumed) cause, it would be expected that these seizures would have a partial onset. Sometimes the partial onset may go unrecognized due to origin from a silent site (eg, frontal or temporal neocortex) or because the patient may not be able to accurately relate the symptoms of partial onset. The diagnosis of complex partial seizures can be a challenge in the elderly, particularly those in LTC facilities. Elderly patients with new-onset complex partial seizures frequently do not have auras, automatisms are less frequent, and the period of postictal confusion may be prolonged.13 These patients may not be able to provide a solid history, and cognitive impairment may hamper recognition of these events. Therefore, transient periods of amnesia or unusual behavior may be difficult to differentiate from other comorbidities.

Because new-onset seizures in the elderly are typically localization-related (partial), they frequently recur. In the VA Cooperative Study 428, even with treatment (there was no placebo group), 39% of the patients had at least 1 seizure in the first year of treatment and 17% had 5 or more seizures. Treatment after the first unprovoked seizure in the elderly is appropriate in most cases, but some exceptions can be made. For example, with a nursing home patient who may have had a nonconvulsive partial seizure or has far advanced Alzheimer’s disease, treatment may worsen symptoms. This approach is different than the case of a child with seizures, in which often no therapy is initiated until after the second seizure.

Therefore, most elderly patients with new-onset seizures should receive AED therapy. Because of the symptomatic nature of most of the seizures in this age group, it is unclear whether any of these patients will be candidates for AED withdrawal. No studies of AED withdrawal in the elderly have been conducted. Even a
single recurrent seizure in an active elderly patient can have a major impact on quality of life. Because long-term therapy should be anticipated, the selection of an AED is important. From the perspective of efficacy, all currently used first- and second-generation AEDs—with the exception of ethosuximide—are effective for partial seizures with or without secondary generalization. As a result, selection can be based on considerations such as tolerability, side-effect profile, and pharmacokinetics—factors that are critical in this age group.

Efficacy Versus Tolerability

Successful treatment of seizures incorporates efficacy and tolerability of the AED(s) selected. In no population is this more important than in the elderly. This concept of successful treatment was incorporated into the early VA Cooperative studies on first-generation AEDs and was the focus of the most recent VA Cooperative Study 428.1,14,15 Other well-designed AED trials tend to focus on measures of efficacy as the primary outcomes because these are pivotal trials, typically in patients with refractory epilepsy, designed to demonstrate efficacy for later regulatory approval of a new drug.

Efficacy Trials of Antiepileptic Drugs in the Elderly

With rare exceptions, well-designed controlled trials (ie, providing class I or II data) of AEDs in the elderly are lacking. In pivotal trials of investigational AEDs, the elderly are typically excluded, as are children and pregnant women. The elderly are frequently taking many other medications, may be more sensitive to medication interactions and side effects, and are more likely to exit from trials (thereby affecting intent-to-treat analyses) for a variety of reasons. For example, in the VA Cooperative Study 428, 7% of the patients exited because of death unrelated to AED use.5

One randomized, double-blind study of AED use in 150 elderly patients with new-onset epilepsy found lamotrigine to be significantly better tolerated than carbamazepine.16 Phase IV unblinded, open-label trials of gabapentin and levetiracetam have also included cohorts of elderly patients.17-19 In the gabapentin trial, 97 of 1055 patients were older than 65 years; in the levetiracetam trial, 65 of 936 patients were older than 65 years. Although these trials were unblinded, nonrandomized trials in outpatient facilities that provide only class III data, the patients had long histories (typically greater than 20 years) of refractory epilepsy; therefore, this reflects different populations than the VA Cooperative Study 428.

In both studies, the responder rates and seizure-free rates (for the limited duration of the study) in the elderly groups were greater than for the entire patient cohort. These differences were not significant; whether this would have occurred with a larger elderly cohort is unknown. Discontinuations caused by adverse events were less than 20% in each trial. Investigators from both studies concluded that these 2 second-generation agents were generally as well tolerated as polypharmacy and equally efficacious in the elderly compared to the entire (predominantly nonelderly) study population.

The recently published VA Cooperative Study 428 was a well-designed, comparative, blinded trial of carbamazepine, gabapentin, and lamotrigine in elderly patients (defined as >60 years of age) with new-onset epilepsy. The trial was begun before US approval of oxcarbazepine or levetiracetam. Almost 600 patients from 18 centers were included in the trial. Carbamazepine was selected as a standard for first-generation AED therapy for partial seizures. No significant differences in efficacy were observed among the 3 agents; approximately 50% of patients were seizure-free at 12 months (Figure 2).5 One of the conclusions from this trial was that lamotrigine and gabapentin
should be considered as initial therapy for elderly patients with new-onset seizures. Although neither of these agents has US Food and Drug Administration (FDA) approval for initial monotherapy, recently published American Academy of Neurology guidelines found that there was reliable class I data to support a Level A recommendation for initial monotherapy in new-onset seizures for each of these drugs. In fact, no AED that is effective as adjunctive therapy has been shown to be ineffective as monotherapy. The limitations on FDA approval for monotherapy are, in part, a reflection of requirements for placebo-controlled trials or controlled trials that can demonstrate a difference between treatments (rather than equivalency trials accepted by regulators in other parts of the world). These difficult trials are thought by many investigators to put the study patients at some risk.

**TOLERABILITY OF ANTIEPILEPTIC DRUGS IN THE ELDERLY**

The major conclusion from the VA Cooperative Study 428 was that adverse drug reactions were a limiting factor in patient retention. Thus, it is appropriate when treating seizures in elderly patients to consider tolerability and efficacy as important factors in successful therapy. Although no controlled trials exist to indicate that second-generation AEDs are more efficacious than first-generation AEDs, experience suggests that selected second-generation AEDs have better tolerability.

It may be difficult to recognize AED toxicity in elderly patients. The VA Cooperative Study 428 observed neurologic impairment among patients at study entry (Table 1). AED effects on cognitive function or gait in this population may go unreported by patients or may be difficult to differentiate from baseline deficits. In the LTC population, even attentive caregivers may not be able to recognize signs of toxicity and patients may also be less able to report them.

Potential cognitive side effects of AEDs are important considerations in patients of all ages, but the elderly may be more sensitive to these effects or have pre-existing cognitive impairment that makes side effects less likely to be recognized or reported. Various trials of gabapentin and lamotrigine in elderly and nonelderly populations have indicated better cognitive profiles than carbamazepine. Recent data on levetiracetam indicate improved performance compared to carbamazepine. In a survey of more than 1200 patients taking a new AED in the outpatient clinic of a major epilepsy center, gabapentin, lamotrigine, and levetiracetam were associated with the fewest self-reported cognitive side effects.

The VA Cooperative Study 428 found that patients were taking an average of 7 additional medications. Other studies have found similar rates of polypharmacy. Not only does this increase the potential for drug interactions, but the potential for additive side effects is present. Antidepressants, antipsychotics, and benzodiazepines are 3 of the most commonly coprescribed agents in elderly nursing home patients taking AEDs.

**PHARMACOKINETICS AND DRUG INTERACTIONS**

The elderly patient, even the healthy patient, will have age-dependent decreases in hepatic and renal clearance, in addition to decreased protein binding. The concept of a “therapeutic range” in the elderly patient needs to be redefined in this context. The typical therapeutic ranges of 10 to 20 µg/mL for phenytoin or 4 to 12 µg/mL for carbamazepine often are inappropriate for the elderly, who may, for a variety of reasons, experience toxicity within the middle to upper therapeutic range. Evidence from nursing home

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**Table 1. New-Onset Geriatric Epilepsy VA Cooperative Study 428: Neurologic Findings at Entry**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Mild cognitive impairment</td>
<td>(35%)</td>
</tr>
<tr>
<td>Abnormal sensory examination</td>
<td>(30.9%)</td>
</tr>
<tr>
<td>Abnormal station</td>
<td>(23.6%)</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>(52.6%)</td>
</tr>
<tr>
<td>Diminished motor power</td>
<td>(22.3%)</td>
</tr>
<tr>
<td>Abnormal coordination</td>
<td>(14.5%)</td>
</tr>
<tr>
<td>Memory problems</td>
<td>(25.8%)</td>
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Data from Rowan et al.
data suggests that the elderly may be more sensitive to medication. A nationwide study has shown that nursing home residents receive lower doses and/or are being maintained at the lower end of or below the “suggested” therapeutic ranges that are used in adults (Figure 3). Although therapeutic ranges for the new AEDs have not been established, many have broader ranges (eg, 3–18 µg/mL for gabapentin and lamotrigine and 10–60 µg/mL for levetiracetam) than the first-generation agents.

In elderly patients, the potential for toxicity with phenytoin is possibly greater than with any other AED because the transition to nonlinear kinetics is steeper in this cohort (Figure 4). A recent study by Birnbaum et al found a large degree of variability in total phenytoin levels in nursing home patients, despite constant daily doses. When one considers that this age group may have signs of toxicity at lower serum levels (eg, at 15 µg/mL) than younger patients and that these signs may go unrecognized, the nonlinear kinetics of phenytoin pose one of the greatest risks for AED toxicity in the elderly.

Many first-generation AEDs (eg, carbamazepine, phenytoin, phenobarbital, and primidone) are powerful inducers of hepatic isoenzymes (CYP1A2, 2C9, C19, and 3A4). In addition, these AEDs are substrates of the hepatic enzymes (Table 2). Therefore, the potential for multiple drug interactions exists between the AEDs and other agents, or if AED polypharmacy is used with first-generation agents. In the elderly cohort, use of enzyme-inducing AEDs with cardiovascular or psychotropic agents (2 important drug classes for this population) can result in interactions leading to a lack of efficacy or the need to significantly increase dosages to achieve the desired effect; this can significantly add to medication costs.

A recent survey of elderly patients with epilepsy in the VA system found that approximately 17% of patients were taking phenobarbital and 54% were taking phenytoin, commenting that these agents were potentially inappropriate for this age group. Additionally, inhibitors of CYP2C9 (eg, amiodarone and fluconazole) can significantly increase phenytoin levels. Inhibitors of CYP3A4 (eg, diltiazem, grapefruit juice, and propoxyphene) can increase carbamazepine levels.

Of the first-generation AEDs, only valproate is not an inducer of hepatic enzymes. Many second-generation agents do not induce hepatic enzymes, and the agents that do induce hepatic enzymes (topiramate and oxcarbazepine) do much less than the first-generation agents, thus they have fewer potential interactions. For example, carbamazepine can have significant effects on oral anticoagulants, whereas oxcarbazepine does not.
COMORBIDITY IN THE ELDERLY: OSTEOPOROSIS

The recent VA Cooperative Study 428 identified hypertension, stroke, and cardiovascular disease as being present in at least 50% of the cohort, which has important implications for comediations and drug interactions. Osteoporosis was not specifically screened for in this population.

Osteoporosis is a common problem in the elderly that affects men and women. Although this condition has become more widely recognized, it is also more common, given the reduced use of routine postmenopausal hormones in women. Loss of bone mineral density (BMD) can be present in varying degrees, progressing from osteopenia to osteoporosis to osteomalacia. An inactive, bedridden elderly patient is at greater risk for bone mineral loss than an active senior patient. The elderly, with or without epilepsy, are at greater risk for falls. Unless fractures occur, osteoporosis is an asymptomatic disorder; therefore, it may go unrecognized unless specific screening is done. The risk of hip fractures is increased as much as 2-fold in patients taking AEDs. The mortality associated with hip fractures in the elderly is approximately 33% in the first year. In a recent study of adult patients (including nonelderly), AED use significantly increased the incidence of osteopenia and osteoporosis compared to control populations, and more than 40% of AED users displayed evidence of significant BMD loss. AED-induced bone loss has been reported in young male populations.

The contributing factors of AED use and BMD loss are complex; many of the studies have been conducted in nonelderly patients. It is generally acknowledged that enzyme-inducing AEDs have the greatest effect and, of these AEDs, it seems that phenytoin is the worst. This may be because phenytoin not only affects vitamin D metabolism but also absorption. However, it is also thought that AEDs can have direct effects on bone turnover in the absence of vitamin D deficiency. In a recent study of 71 women aged 18 to 40 years who took AEDs for longer than 6 months, phenytoin—but not carbamazepine, lamotrigine, or valproate—produced significant BMD loss in just 1 year. A study of 30 elderly men (mean age of 76 years) taking phenytoin or carbamazepine found on BMD scans that 39% had osteopenia and 17% had osteoporosis; all were previously undiagnosed. A recent study of active elderly women found that continuous phenytoin use led to an approximately 2-fold increase in bone loss; this was calculated to increase the risk of a hip fracture by 29% over a 5-year period. There are limited data on the effects of the new AEDs on bone metabolism and turnover. Lamotrigine has the best data, suggesting it does not potentiate osteoporosis. Whether lack of enzyme induction prevents effects on bone mineral turnover is not yet determined. Conflicting results exist for the noninducing AED valproate, and animal studies suggest that zonisamide may affect BMD. Thorough studies on the effects of many of the second-generation AEDs and BMD are lacking.

All elderly patients taking enzyme-inducing AEDs should also take supplemental vitamin D and calcium, unless contraindicated. Currently, it is appropriate to screen all patients older than 60 years for BMD loss. Those patients with osteopenia should be closely observed. In patients with osteopenia or osteoporosis who are taking enzyme-inducing AEDs, particularly phenytoin, consideration should be given to changing AEDs, weighing the risks of osteoporosis with the risk of a breakthrough seizure during AED

<table>
<thead>
<tr>
<th>Table 2. Antiepileptic Drugs and Hepatic CYP Isoenzymes</th>
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<tbody>
<tr>
<td>- Carbamazepine, phenytoin, and phenobarbital induction of CYP1A2, CYP2C9, CYP19, and CYP3A4 can reduce levels of these substrates:</td>
</tr>
<tr>
<td>- Psychoactive medications: amitriptyline, citalopram, clozapine, haloperidol, nortriptyline, olanzapine, paroxetine, risperdone, sertraline, and venlafaxine</td>
</tr>
<tr>
<td>- Cardiovascular drugs: amiodarone, atorvastatin, diltiazem, lovastatin, nifedipine, metoprolol, propranolol, quinidine, simvastatin, timolol, and verapamil</td>
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<tr>
<td>- Nonsteroidal anti-inflammatory drugs</td>
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<tr>
<td>- Warfarin, theophylline, and oral contraceptives</td>
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<tr>
<td>- Protease inhibitors for HIV</td>
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<tr>
<td>- Cyclophosphamide, BCNU, and tamoxifen</td>
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changes. Ideally, appropriate AED selection early in therapy can reduce the risk of increased BMD loss. Additionally, more aggressive therapy to reverse BMD loss also should be considered along with periodic dual energy X-ray absorptiometry scans. It has been suggested that serum calcium levels may correlate with BMD loss; one can also measure levels of 25(OH) vitamin D.

**CHOOSING AN ANTIEPILEPTIC DRUG FOR THE SENIOR PATIENT**

The ideal AED would be one with linear kinetics, no drug interactions, an excellent safety record, no adverse cognitive effects, no undesirable side effects, and the ability to be rapidly introduced. In some patients, the availability of certain formulations (eg, liquid and sprinkle) may be important. Table 3 lists available formulations for the current AEDs.

**FIRST-GENERATION AGENTS**

Phenobarbital and primidone, in addition to being significant inducers of hepatic enzymes, have serious side effects. In the initial VA Cooperative Study, primidone had the greatest number of dropouts because of side effects. Because of the side effects of these agents, neither should be a choice for early treatment of the senior patient with epilepsy. Patients already taking these agents should be carefully assessed for possible adverse cognitive effects. If concern exists, switching to another AED should be considered, again weighing the potential benefits with any risk of seizure recurrence.

Phenobarbital does have the advantages of low cost and a long half-life (approximately 100 hours) that allows once-daily dosing. However, the therapeutic range of 15 to 40 µg/mL should be disregarded in the elderly, and only low doses should be used if the agent is used at all in this population.

Phenytoin remains the most widely prescribed AED in patients older than the age of 60 years or in nursing homes. However, because of concerns about drug interactions, osteoporosis, nonlinear kinetics, and toxicity (eg, ataxia) that may go unnoticed, it is not an ideal agent for this age group. Because the first treating physician (emergency department and primary care) is familiar with phenytoin and desires an agent that can be rapidly introduced (phenytoin and its congener fosphenytoin are available as parenteral formulations), phenytoin is often chosen as initial therapy. In theory, if none of the above concerns is present, phenytoin can be used in low doses with a target serum range of no more than 15 µg/mL. It is also helpful to check a phenytoin free fraction (the unbound active fraction or unbound phenytoin concentration/total phenytoin concentration) in the individual patient and to monitor for osteoporosis. Unfortunately, in practice, the potential problems with phenytoin may go unrecognized and its potential for future effects will persist. Its many disadvantages precluded phenytoin from being one of the study group drugs in the VA Cooperative Study 428.

Carbamazepine is a commonly used drug for the treatment of complex partial seizures. Its use is supported by the results of the early VA Cooperative studies. Carbamazepine induces liver metabolism of other drugs, in addition to itself (autoinduction). It also has an active metabolite (CBZ-10,11-epoxide) that can contribute to its toxicity potential and its efficacy. The potential for cognitive side effects is greater with carbamazepine than with some of the newer AEDs. Drug interactions and potentiation of osteoporosis also remain concerns. It was the first first-generation agent in the VA Cooperative Study 428. Investigators found that, despite a slow titration (200 mg/week to a target dose of 600 mg/day), slower than many neurologists use in practice to allow for hepatic induction, there were significantly more withdrawals because of adverse events in this group than with the 2 second-generation AEDs.

Of the first-generation AEDs, valproate may have the best pharmacokinetic profile, with no hepatic induction. It is highly (>90%) protein-bound, thus it may displace other highly protein-bound drugs. When valproate is used as cotherapy with phenytoin (also highly protein-bound) in elderly patients, phenytoin may be displaced by valproate, although the total phenytoin may fall. However, a small increase in free phenytoin may occur due to inhibition of phenytoin metabolism by valproate. Valproate also may increase phenobarbital levels. A broad-spectrum agent, valproate is useful for patients entering their senior years with primary generalized seizures. The risk of hepatic toxicity is extremely low in the adult patient (<1:700 000 as monotherapy). At high serum levels (80–150 µg/mL), a fine action tremor is common, but this is dose-dependent and infrequent (<10%) at low serum levels (25–50 µg/mL). In the patient with a significant tremor, low

**SECOND-GENERATION AGENTS**

Lamotrigine is a newer AED with a linear kinetic profile, few drug interactions, a long half-life (4–8 days), and no adverse cognitive effects. Its use is beneficial in patients with complex partial seizures. The therapeutic range in the elderly is 4–14 µg/mL. A lower dose range (2.5–7.5 µg/mL) is recommended for patients with renal insufficiency (creatinine level >2 mg/dL). Lamotrigine is not recommended in the elderly with a creatinine clearance <20 mL/min due to the risk of nephrotoxicity. Lamotrigine has been associated with a risk of rash and severe skin reactions in children and adolescents. No increased risk of rash, severe skin reactions, or death has been noted in elderly patients.

Lacosamide is a newer AED with a linear kinetic profile, few drug interactions, and no adverse cognitive effects. Its use is beneficial in patients with complex partial seizures. The therapeutic range is 50–200 µg/mL, and the dose should be increased slowly due to the development of ataxia. Lacosamide is not recommended in the elderly with a creatinine clearance <20 mL/min due to the risk of nephrotoxicity. Lacosamide has been associated with a risk of rash and severe skin reactions in children and adolescents. No increased risk of rash, severe skin reactions, or death has been noted in elderly patients.

Oxcarbazepine is a newer AED with a linear kinetic profile, few drug interactions, and no adverse cognitive effects. Its use is beneficial in patients with complex partial seizures. The therapeutic range is 40–120 µg/mL, and the dose should be increased slowly due to the development of ataxia. Oxcarbazepine is not recommended in the elderly with a creatinine clearance <20 mL/min due to the risk of nephrotoxicity. Oxcarbazepine has been associated with a risk of rash and severe skin reactions in children and adolescents. No increased risk of rash, severe skin reactions, or death has been noted in elderly patients.

**THIRD-GENERATION AGENTS**

Rufinamide is a newer AED with a linear kinetic profile, few drug interactions, and no adverse cognitive effects. Its use is beneficial in patients with complex partial seizures. The therapeutic range is 250–300 µg/mL, and the dose should be increased slowly due to the development of ataxia. Rufinamide is not recommended in the elderly with a creatinine clearance <20 mL/min due to the risk of nephrotoxicity. Rufinamide has been associated with a risk of rash and severe skin reactions in children and adolescents. No increased risk of rash, severe skin reactions, or death has been noted in elderly patients.

Zonisamide is a newer AED with a linear kinetic profile, few drug interactions, and no adverse cognitive effects. Its use is beneficial in patients with complex partial seizures. The therapeutic range is 7.5–100 µg/mL, and the dose should be increased slowly due to the development of ataxia. Zonisamide is not recommended in the elderly with a creatinine clearance <20 mL/min due to the risk of nephrotoxicity. Zonisamide has been associated with a risk of rash and severe skin reactions in children and adolescents. No increased risk of rash, severe skin reactions, or death has been noted in elderly patients.

**FOURTH-GENERATION AGENTS**

Levetiracetam is a newer AED with a linear kinetic profile, few drug interactions, and no adverse cognitive effects. Its use is beneficial in patients with complex partial seizures. The therapeutic range is 1500–3000 µg/mL, and the dose should be increased slowly due to the development of ataxia. Levetiracetam is not recommended in the elderly with a creatinine clearance <20 mL/min due to the risk of nephrotoxicity. Levetiracetam has been associated with a risk of rash and severe skin reactions in children and adolescents. No increased risk of rash, severe skin reactions, or death has been noted in elderly patients.

Topiramate is a newer AED with a linear kinetic profile, few drug interactions, and no adverse cognitive effects. Its use is beneficial in patients with complex partial seizures. The therapeutic range is 500–1900 µg/mL, and the dose should be increased slowly due to the development of ataxia. Topiramate is not recommended in the elderly with a creatinine clearance <20 mL/min due to the risk of nephrotoxicity. Topiramate has been associated with a risk of rash and severe skin reactions in children and adolescents. No increased risk of rash, severe skin reactions, or death has been noted in elderly patients.

Zonisamide is a newer AED with a linear kinetic profile, few drug interactions, and no adverse cognitive effects. Its use is beneficial in patients with complex partial seizures. The therapeutic range is 7.5–100 µg/mL, and the dose should be increased slowly due to the development of ataxia. Zonisamide is not recommended in the elderly with a creatinine clearance <20 mL/min due to the risk of nephrotoxicity. Zonisamide has been associated with a risk of rash and severe skin reactions in children and adolescents. No increased risk of rash, severe skin reactions, or death has been noted in elderly patients.
### Table 3. Formulations, Routes of Administration, Strengths, Routes, and Special Problems of Maintenance Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Available Formulations</th>
<th>Strength (mg or mg/mL if liquid)</th>
<th>Possible Routes: Primary and Alternates</th>
<th>Special Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine⁵¹⁻⁵³</td>
<td>Tablet</td>
<td>200</td>
<td>PO</td>
<td>Generic available. Prolonged absorptive phase with variable (T_{\text{max}}); induction results in earlier (T_{\text{max}}). Earlier (C_{\text{max}}) results in higher (C_{\text{max}}) which can produce transient side effects. Tablet must be swallowed whole; do not crush or chew. Capsules may be opened and the beads sprinkled over food; capsules should not be crushed or chewed.</td>
</tr>
<tr>
<td></td>
<td>Chewable tablet</td>
<td>100, 200</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suspension</td>
<td>100 mg/5mL</td>
<td>PO, R</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extended-release tablet</td>
<td>100, 200, 400</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extended-release capsule</td>
<td>100, 200, 300</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>Tablet</td>
<td>400, 600</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suspension</td>
<td>600 mg/5mL</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>Injectable</td>
<td>50 mg/PE mL</td>
<td>IV, IM</td>
<td>Product needs to be stored at 2–8˚C. Fosphenytoin concentrations after IM administration are lower but more sustained than those after IV administration due to the time required for absorption of the fosphenytoin from the injection site. Gabapentin bioavailability decreases as dose increases; generic available.</td>
</tr>
<tr>
<td>Gabapentin⁵⁴⁻⁵⁵</td>
<td>Capsule</td>
<td>100, 300, 400</td>
<td>PO</td>
<td>Solution needs to be stored at 2–8˚C.</td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td>600, 800</td>
<td>PO</td>
<td>Doses may need to be adjusted for patients with renal impairment.</td>
</tr>
<tr>
<td></td>
<td>Solution</td>
<td>250 mg/5mL</td>
<td>PO</td>
<td>Unpleasant taste, rejected by many; generic available.</td>
</tr>
<tr>
<td>Lamotrigine⁵⁶⁻⁵⁸</td>
<td>Compressed tablet</td>
<td>25, 100, 150, 200</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dispersible tablet</td>
<td>2, 5, 25</td>
<td>PO, R</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam⁵⁹⁻⁶⁰</td>
<td>Tablet</td>
<td>250, 500, 750</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine⁶¹⁻⁶²</td>
<td>Solution</td>
<td>150 mg/mL</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital⁶³</td>
<td>Tablet</td>
<td>20 mg/mL</td>
<td>PO, R</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Injectable</td>
<td>15, 30, 60, 100</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Phenytoin⁶³</td>
<td>Suspension (phenytoin acid)</td>
<td>25 mg/mL</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chewable tablet</td>
<td>50</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prompt-release capsule (phenytoin acid)</td>
<td>100</td>
<td>PO</td>
<td></td>
</tr>
</tbody>
</table>

(Continued on page S204)
doses of valproate should be used or alternative AEDs considered. Recent reports suggest that the weight gain seen in some patients taking valproate may be less prevalent in the elderly. Valproate may be the best of the first-generation agents for use in the elderly. Valproate also is available in sustained-release and parenteral formulations.

**SECOND-GENERATION AGENTS**

The recent VA Cooperative Study 428 selected gabapentin and lamotrigine as the 2 second-generation agents for comparison with carbamazepine. As mentioned earlier in this article, this trial was begun before oxcarbazepine and levetiracetam were approved in the United States; a trial comparing carbamazepine with levetiracetam in new-onset geriatric epilepsy is under way.

Gabapentin and lamotrigine have the advantages of lower to no enzyme-induction capabilities, positive cognitive profiles, and strong safety profiles. Gabapentin is an extremely safe agent; if lamotrigine is titrated slowly, the risk of a serious hypersensitivity reaction (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis) is only approximately 1:2500 for new users—no greater than phenobarbital or phenytoin and not significantly greater than carbamazepine. Lamotrigine levels can be significantly

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**Table 3. Formulations, Routes of Administration, Strengths, Routes, and Special Problems of Maintenance Antiepileptic Drugs**

(Continued from page S203)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Strengths</th>
<th>Routes</th>
<th>Special Problems of Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>Capsule 25, 50, 75, 100, 150, 200, 225, 300</td>
<td>PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>Suspension 250 mg/5 mL (50 mg/mL)</td>
<td>PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Tablet 50, 250</td>
<td>PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Tablet 25, 50, 100, 200</td>
<td>PO, R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>Capsule 250</td>
<td>PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enteric-coated tablet 125, 250, 500</td>
<td>PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sprinkle capsules 125</td>
<td>PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extended-release capsule 250, 500</td>
<td>PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syrup 100 mg/mL</td>
<td>PO, R</td>
<td>IV</td>
<td>Valproate has an objectionable aftertaste.</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Capsule 25, 50, 100</td>
<td>PO</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IM = intramuscular; IV = intravenous; PO = by mouth; R = by rectum.
lowered by agents that induce hepatic enzymes.\textsuperscript{82} Lamotrigine also can have broad-spectrum efficacy, including some primary generalized epilepsies.\textsuperscript{83}

Pregabalin, a congener of gabapentin, recently has been approved for the treatment of partial seizures.\textsuperscript{84,85} Although the double-blind controlled trials demonstrate efficacy that is much greater than that seen with gabapentin (in intermediate-dose trials), pregabalin shares some non–efficacy-related benefits with gabapentin. It is renally excreted, thus it has no effects on other medications, does not induce hepatic enzymes, and is not affected by other agents.\textsuperscript{86} Whether it will share the same safety and cognitive profiles with gabapentin is hoped but not yet determined. Pregabalin has linear kinetics throughout the dose range of 50 to 600 mg/day (gabapentin is non-linear at higher doses) and is approved for twice-daily dosing or thrice-daily dosing. Pregabalin has many characteristics that make it a potentially favorable agent for use in elderly patients with seizures. There is already considerable experience with pregabalin in the elderly as part of controlled trials in diabetic and postherpetic neuralgia. Peripheral edema and weight gain have been reported in a small percentage of patients taking pregabalin.\textsuperscript{87-89} The agent is a schedule V drug.

Levetiracetam is another second-generation agent with several advantages for use in the elderly patient. It can be introduced rapidly at therapeutic doses when needed, has linear kinetics, no hepatic induction, a good cognitive and side-effect profile, and no known interactions with other medications. Similar to gabapentin and pregabalin, it is not affected by other medications, is not metabolized by hepatic enzymes, and is predominantly renally excreted (dose reductions of renally excreted AEDs need to be made when there is significant renal impairment). Levetiracetam also appears to be a broad-spectrum agent with efficacy beyond partial seizures.\textsuperscript{83} In addition, a parenteral formulation is in development and approval is anticipated soon. Behavioral side effects, most commonly described as irritability, can be seen in 10% to 15% of patients, but some of these effects are transient initiation effects. Studies suggest that discontinuation of levetiracetam because of behavioral side effects is less than 7%.\textsuperscript{91} Preliminary studies in the elderly have shown it to be well tolerated in this group.\textsuperscript{83,95}

Oxcarbazepine has not been associated with any of the hematologic effects (minor or serious) observed with carbamazepine. Extensively tested, oxcarbazepine has approval for initial monotherapy and adjunctive therapy of partial and secondarily generalized seizures. Studies indicate improved tolerability compared to carbamazepine.\textsuperscript{96} Although well tolerated in the elderly, the incidence of significant hyponatremia (<125 mEq/L) is approximately 6%.\textsuperscript{97} Whether hyponatremia, which may be asymptomatic, is more likely in patients taking diuretics or can be predicted from early electrolyte screening is not established.

Tiagabine is a new AED that does not induce hepatic enzymes but is affected by enzyme-inducing agents. Reports of its use in the elderly are limited.\textsuperscript{98} Topiramate and zonisamide are potential broad-spectrum agents. Topiramate also recently received approval for initial monotherapy in partial-onset or primary GTCS. These agents have less favorable cognitive profiles compared to other second-generation AEDs and may facilitate weight loss, which may not be desirable in the elderly population.\textsuperscript{99,100} If these agents are used in the elderly, they should be introduced and titrated slowly.

\textbf{Polypharmacy with AEDs in the Elderly}

Many elderly patients can have their seizures controlled with AED monotherapy, but others may require polytherapy. AED polytherapy increases the potential for drug interactions, not only with other drugs but also among the AEDs. A recent study by Harms et al of 3881 nursing home patients taking AEDs found that 370 (9.5%) were on polypharmacy and, of these patients, 72% were taking problematic combinations with the potential for undesirable pharmacokinetic or pharmacodynamic interactions.\textsuperscript{101} The combination of phenytoin plus phenobarbital or primidone, which is metabolized to phenobarbital, was found in 33% of patients on AED polytherapy. These were the most common combinations.

The agents have significant potential for additive side effects and toxicity, in addition to increased induction of hepatic enzymes. Additionally, phenytoin can reduce phenobarbital levels, and chronic phenobarbital may also induce phenytoin metabolism (after acutely inhibiting it). Any elderly patient on AED polypharmacy should have a careful review of therapy to determine if monotherapy can provide similar seizure control, as it often can.\textsuperscript{102} If AED polypharma-
cy is required, agents should be selected that have different mechanisms of action, are less likely to interact, and are less likely to produce additive toxicity, with the understanding that polypharmacy always has some increased risk for added toxicity in the elderly.

**Considerations in the Patient with Well-Controlled Seizures but Side Effects**

Physicians are often reluctant to consider changes in AEDs for patients with well-controlled seizures, even if they are experiencing side effects, because of the concern that seizure control may be sacrificed. With the patient who has been readily controlled on the first AED administered, this concern is probably unwarranted. Studies by Kwan and Brodie of adult patients presenting with new-onset seizures found that 50% were readily controlled on low or modest AED doses and that it did not seem to matter which AED (new or old) was chosen, provided it was appropriate for the seizure type. In the VA Cooperative Study 428, 219 of 593 patients (37%) entering the trial were taking phenytoin, which was then discontinued as the patients were randomized to one of the study drugs.5 In patients who are readily controlled, consideration should be given to changes in AED therapy if side effects are present. There is a small risk of loss of control, but the potential benefits for quality of life may be significant. Seizures are episodic events, but side effects are often continuous.

**The Role of the Nurse and Pharmacist**

The roles of nurses and pharmacists in the care of elderly patients with seizures are extremely important, particularly in LTC facilities, but also during acute hospitalizations. Nurses, because of the time they spend with the patient, have the potential to identify signs of AED toxicity that may go unrecognized by the physician on rounds. Pharmacists, on the other hand, have the expertise to alert the treating physician about potential drug interactions.

**When to Refer to a Neurologist**

When a child or young adult first experiences a seizure, often a neurologist is involved early in the evaluation and treatment decision. In the elderly patient with new-onset seizures, this may be less likely to occur, in part because most elderly patients have established primary caregivers for known medical problems or routine care. In cases in which the diagnosis of seizure type is determined, often non-neurologists will initiate care with first-generation AEDs and reserve neurologic consultation for those patients who do not respond to the first agent selected. Unfortunately, because seizures in the elderly are often readily controlled regardless of the AED selected, these patients may remain on AEDs that, for reasons enumerated earlier in this article (eg, drug interactions, cognitive side effects, and osteoporosis), may not be the best choice for long-term treatment. It is hoped that as the second-generation agents no longer are considered “new,” primary caregivers will consider selecting from the spectrum of AEDs available.

One could argue that a neurological consultation would be ideal following the first seizure in most elderly patients, if only to assist in the selection of the most appropriate AED. Certainly, a neurologist should be involved if the diagnosis is in question, the patient continues to have seizures, or drug intolerance is exhibited. Although these elderly patients typically need lifelong therapy, routine management can be done by the primary caregiver after appropriate assessment and initiation of treatment.

**Conclusions**

In this era of new AEDs, treating physicians are searching for the appropriate use of these second-generation agents. Although some drugs may offer advantages to patients who have failed to have their seizures controlled by other AEDs, we cannot definitively determine that the new AEDs are more effective than the older agents. However, what is becoming apparent is that several of the second-generation AEDs have better pharmacokinetic and side-effect profiles compared to first-generation AEDs and that this can result in improved tolerability and fewer side effects. In no patient population is the issue of comediations and comorbidity more important than in the senior population. This subpopulation has the greatest incidence of new-onset epilepsy and these patients will typically need lifelong therapy.

The recently published VA Cooperative Study 428 has the best evidence to date to show support for the concept that in elderly patients with epilepsy, certain second-generation AEDs may offer distinct advantages over first-generation agents. Selected second-generation agents have been preferred by epilepsy experts since at
least 2000, with lamotrigine, levetiracetam, and gabapentin being the most commonly suggested in the healthy or ill elderly patient. Use of these new AEDs as initial or early therapy in elderly patients can now be more strongly advocated, but implementation will require further educational initiatives directed toward the physicians who initially treat these patients.

The content in this monograph was developed with the assistance of a medical writer. Each author had final approval of his/her article and all its contents.

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