

EPILEPSY IN THE OLDER ADULT



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LEARNING OBJECTIVES

1. Distinguish between a seizure, nonepileptic seizure, and epilepsy given a description of a patient and his/her clinical symptoms.
2. Recognize and manage the etiologies and risk factors for seizures in older adults.
3. Develop an appropriate pharmacotherapy treatment plan for an older adult patient with newly diagnosed epilepsy.
4. Design an effective plan for monitoring antiepileptic drug (AED) therapy in older adult patients.
5. Minimize and manage common adverse effects of AEDs in the older adult.
6. Detect and manage important interactions between AEDs and other medications.
7. Design a plan for discontinuation of AEDs when appropriate.

INTRODUCTION

Epilepsy is a very common neurologic disorder, affecting 1% to 2% of the U.S. population. The incidence of seizures and new-onset epilepsy increases greatly in adults older than 65 years. However, the detection and diagnosis of epilepsy in older adults are complicated by a clinical presentation different from that in younger individuals, an increased incidence of cognitive impairment

that makes seizure detection difficult, and a lack of recognition that epilepsy is a problem in older adults.

Pharmacotherapy is the mainstay of epilepsy treatment, especially in the older adult population. Although antiepileptic drugs (AEDs) are generally effective in the treatment of seizures, the use of AEDs is complicated in older adults by changes in physiology and in the disposition of drugs, adverse effects that are especially problematic, and drug interactions that can be difficult to manage. In addition, the etiologies of epilepsy in older adults necessitate decisions about the initiation and discontinuation of pharmacotherapy that are different from those in younger patients. These factors combine to make the pharmacotherapeutic management of older adult patients with epilepsy a challenge that requires a high level of understanding of the disease process, the unique features of older adults, and the use of AEDs in this age group.

Epidemiology in the Older Adult

The incidence of unprovoked seizures and epilepsy is bimodal, usually occurring in children younger than 5 years and in adults older than 65 years. The incidence of unprovoked, repeated seizures rises rapidly for individuals older than 65 years, ranging from 85 to 135 per 100,000 people. This is in comparison to rates of 15–30/100,000 individuals in the 20-year to 64-year age group. Increased incidence rates are thought to be

BASELINE REVIEW RESOURCES

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*, 7th ed. Boston: McGraw-Hill, 2008:chaps 58, 59.
- American Epilepsy Society. Epilepsy Education Program. Available at www.aesnet.org/go/professional-development/educational-opportunities/epilepsy-education-program/epilepsy-education-program. Accessed May 10, 2011.
- Wyllie E, Cascino GD, Gidal BE, Goodkin HP, eds. *Wyllie's Treatment of Epilepsy, Principles and Practice*, 5th ed. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins, 2011.

ABBREVIATIONS IN THIS CHAPTER

AED	Antiepileptic drug
EEG	Electroencephalography
TDM	Therapeutic drug monitoring

related to increased rates of cerebrovascular events, dementia, trauma, and neurodegenerative disorders in older adults.

Etiology in the Older Adult

Up to 50% of new-onset seizures and epilepsy in the older adult population are caused by stroke, either hemorrhagic or ischemic. Development of epilepsy after a stroke is associated with several factors, including type of stroke, localization, and severity. Hemorrhagic strokes have the greatest propensity to cause seizures, followed by embolic and then thrombotic ischemic strokes. Strokes that involve the cortex have higher seizure rates than do subcortical strokes.

As might be expected, more severe strokes, as determined through various clinical and neuroimaging criteria (e.g., the NIH [National Institutes of Health] Stroke Scale or the Modified Rankin Scale), are associated with an increased risk of seizures and epilepsy. The risk of epilepsy in the first year after a stroke is up to 20 times greater than in individuals who have not experienced a stroke. In addition, individuals with a history of epilepsy are more likely to experience a stroke.

Traumatic brain injuries are the next most common cause of seizures and epilepsy in older adults. Around 20% of older adults with new-onset epilepsy have a temporally related traumatic brain injury. Predictive factors identified for the development of epilepsy caused by a traumatic brain injury in this age group are brain contusion with subdural hematoma, skull fracture, and loss of consciousness.

Tumors and dementia are also common causes of epilepsy in older adults. Up to one-third of seizures in older adults are caused by tumors. The risk seems to be higher with primary and low-grade tumors than in secondary and high-grade tumors. Even relatively small tumors can cause seizures, and the surgical resection of tumors does not appear to greatly alter epileptogenesis. Similar to tumors, dementia is associated with disruption and degeneration of neuronal pathways. Several prospective observational studies have explored the relationship between seizures and dementia. The risk of seizures seems to be highest in individuals with more severe dementia and in those who develop dementia at a younger age.

Underlying toxic, metabolic, and infectious disorders can result in seizures. Without treatment of these

problems, pharmacotherapy with AEDs will be less effective in controlling seizures. The main toxic events that result in seizures in older adults are adverse reactions to drugs, abuse of illicit or prescription medications, and alcohol withdrawal. A thorough medication history, including recently discontinued drugs, use of over-the-counter medications, use of herbal medications, possible abuse of medications, and alcohol consumption, is important in the assessment of a patient with new-onset seizures. Although not often considered in the assessment of older adults, urine toxicologic screening is especially helpful in detecting potential toxic causes of seizures and should be routinely performed.

Hyponatremia and hypoglycemia are the most common metabolic disturbances in older adults that can result in seizures. Diuretic use can result in hyponatremia, and serum sodium should be evaluated in patients with seizures. If hyponatremia is detected, sodium replacement should be given before initiating an AED. Hypoglycemia is an issue for patients treated for diabetes and should be corrected before initiating AEDs for seizures. Meningitis and encephalitis can also result in seizures, necessitating the use of appropriate antimicrobial treatment. Unnecessary use of AEDs can be prevented by identifying the underlying pathology and initiating specific therapy for the underlying disorder.

Risk Factors

Most risk factors for epilepsy in the older adult are risk factors for the primary etiologies of epilepsy in this age group. For example, stroke is the most common etiology for epilepsy in older adults. Management of risk factors for stroke (e.g., hypertension, smoking, atrial fibrillation) should be implemented to reduce the possibility of older adults developing epilepsy. Because traumatic brain injuries are a common cause of epilepsy in the older adult, and because falling is the most common cause of trauma in this age group, the prevention of falls will reduce the risk of older adults developing epilepsy.

PHARMACOTHERAPY

In contrast to younger individuals who have several possible treatment options (e.g., epilepsy surgery), the older adult with epilepsy essentially has only one treatment option available, pharmacotherapy. This limitation in treatment options is because of the increased risk of adverse outcomes associated with surgery in older individuals. In older adults who experience a seizure, an accurate diagnosis and determination of the recurrence risk are integral to decisions about appropriate pharmacotherapy. Once an accurate diagnosis is made, selecting a specific drug to be used for treatment must be made with several factors in mind. These factors range from choice of AEDs, with respect to seizure type; to

adverse reactions that may limit the effectiveness of a particular drug and potential drug interactions. After initiating pharmacotherapy with an AED, it is essential to provide careful monitoring of seizure frequency and adverse effects to ensure the proper medical management of the older adult patient with epilepsy.

Accurate Diagnosis

The first major decision point, making an accurate diagnosis of seizures and epilepsy, can be a difficult process with the older patient. Symptoms of seizures in older adults are often vague, nondescript neurologic complaints. Patients may have brief lapses in memory, temporary behavioral changes, or minor involuntary movements in a limb or other part of the body. More prominent features of seizures such as generalized tonic-clonic seizures are relatively rare, making seizures difficult to detect.

Other patient factors further complicate the identification of seizures. From a social perspective, many in this age group live alone, so no other individuals are available to regularly observe brief events such as seizures. Common cognitive or memory impairments can also make recollection of seizure events or descriptions of these events unreliable. Of importance, pharmacists working with older adults should carefully gather information about possible seizures from several sources and not depend on the patient as the sole source of information. When possible, neighbors, family members, caregivers, or others who have an opportunity to observe the patient should be consulted for an accurate description and accounting of potential seizure events.

Symptoms of common diseases in this age group can also mimic seizures. Cardiac arrhythmias, falls, global transient amnesia, myoclonus, orthostatic hypotension, REM (rapid eye movement) sleep behavior disorder, restless leg syndrome, syncope, transient ischemic attack, and tremor all have features that may be confused with seizures. For example, brief cardiac arrhythmias may cause episodes of acute loss of consciousness, with motor activity that appears similar to seizures; transient ischemic attacks often produce neurologic symptoms such as numbness, tingling, and altered consciousness, all of which can be features of seizures. Even simple falls can be mistaken for seizures. As part of the diagnostic workup of an older adult with possible seizures, an accurate medical history is needed, with consideration given to other possible diseases that appear to be seizures. Before making a diagnosis of epilepsy, alternative explanations for seizure-like events must be considered and ruled out.

Diagnostic Criteria

Because the diagnosis of epilepsy in older adults is complicated by several factors, attempts have been made to establish diagnostic criteria. A recently published

study established a diagnostic algorithm for epilepsy in older adults. The findings from an extensive literature review were applied in a large review of patient charts and followed by a logistic regression analysis. From this, the authors were able to identify three major and four minor diagnostic criteria. The major criteria were confusional state with sudden onset, rhythmic muscular contractions in a focal territory, and paroxysmal behavioral disorder associated with a focal neurologic sign. Minor criteria were impairment of consciousness, isolated paroxysmal behavioral disorder, history of epilepsy, and focal slow waves on electroencephalography (EEG). A diagnosis of epilepsy in the older adult can be made if at least one major criterion is present or two or more minor criteria are present. The sensitivity and specificity for this algorithm were reported to be 84.8% and 88.6%, respectively.

This study shows that a thorough, careful history is the most important aspect of establishing a diagnosis of epilepsy in older adults. Neuroimaging and prolonged video EEG monitoring may be useful in ruling out underlying causes of seizures or ensuring that unusual neurologic events are seizures. However, the diagnosis of epilepsy can be based on the application of these diagnostic criteria, in contrast to what is usually involved in the diagnostic workup of a younger individual.

Seizure vs. Psychogenic Nonepileptic Seizures

Psychogenic nonepileptic seizures can be easily mistaken for epilepsy because they are repeated, stereotypical spells that clinically appear to be seizures. However, during these spells, EEG patterns remain normal.

A recent case series of 469 patients who were assessed and given a diagnosis of nonepileptic events showed that more than 15% of these individuals were older than 55 years. Of these, more than 80% had both epilepsy and nonepileptic events, making diagnosis and treatment even more difficult. A history of sexual abuse or minor head trauma was most often associated with the occurrence of psychogenic nonepileptic seizures. Of most concern was that more than 90% of the older adult patients with this diagnosis received several AEDs before being given a diagnosis of psychogenic nonepileptic seizures. Depression or anxiety disorders were identified in more than 50% of these individuals, and 90% had somatoform disorders identified through a Minnesota Multiphasic Personality Inventory. During video monitoring, the most common clinical symptoms of psychogenic nonepileptic seizures were waxing and waning tremors or shaking of the extremities, rocking of the body, bicycling movement of the legs, pelvic thrusts, thrashing movements, cheek biting, and unusual dystonic postures. Most patients were unresponsive or very slow in response during these spells.

The definitive diagnosis of psychogenic nonepileptic seizures is accomplished through 24-hour video EEG

monitoring. During this procedure, the goal is to capture several of the patient's typical spells on video to characterize the clinical presentation and simultaneous EEG recording. Absence of EEG changes during a typical spell results in a diagnosis of psychogenic nonepileptic seizures. Video EEG monitoring should be considered in an older adult who continues to have seizure-like events despite adequate monotherapy treatment with at least two AEDs. Treatment of these spells typically involves psychiatric and psychological interventions, including the potential use of antidepressants, antipsychotics, and/or cognitive behavior therapy. The use of AEDs, except for psychiatric indications, is not effective for the treatment of nonepileptic events and should be avoided. If the patient is receiving an AED, it should be gradually tapered and discontinued unless needed for psychiatric indications or for epileptic seizures. A patient with this diagnosis should be referred for psychiatric evaluation and management. For individuals who have epileptic and nonepileptic seizures, patients and caregivers are educated to differentiate between the various spells.

Isolated Seizure vs. Epilepsy

It is important to determine whether a seizure is an isolated event or one that will recur and become epilepsy. This is a key decision point in determining the need for pharmacotherapy. Recurrence rates of a seizure are much higher in the older adult than in the younger adult, with a 70% to 80% chance of a seizure recurring after the first event. Because of this high recurrence rate, most recommendations for treating seizures in older adults encourage the use of an appropriate AED, even after a single seizure (Figure 1-1).

Because of the high recurrence rate and apparently good response to AEDs at rather low to moderate doses, most physicians and pharmacists prefer to begin treatment with AEDs if diagnostic criteria for a seizure are met. However, in making this decision, the overall efficacy of various agents and the risk of adverse effects should be considered and weighed against the risk of recurrent seizures.

Decision to Treat

Efficacy

Three blinded efficacy studies of older adults compared carbamazepine, lamotrigine, and, in one study, gabapentin. The first study included 150 patients older than 65 years with newly diagnosed epilepsy. Randomization was to lamotrigine or regular-release carbamazepine. A significantly greater percentage of patients taking lamotrigine (71%) remained in the study compared with patients taking carbamazepine (42%). Patients taking carbamazepine were twice as likely to withdraw from the study, primarily because of adverse events. There was no difference in the percentage of patients becoming seizure free.

A follow-up study compared lamotrigine with extended-release carbamazepine using a similar protocol. No difference was detected at the study's end, with 73% of remaining patients (n=93) taking lamotrigine and 67% taking extended-release carbamazepine (n=92). Subjects had a mean age of 74 years, and adverse event rates were almost identical between the two groups, as were the seizure-free rates. It appears that the differences in withdrawal and adverse event rates between lamotrigine and regular-release carbamazepine can be alleviated with an extended-release carbamazepine product.

The final study was a three-way blinded trial comparing lamotrigine, regular-release carbamazepine, and gabapentin. Significantly more individuals taking carbamazepine exited the study than those taking lamotrigine or gabapentin, and more adverse events occurred with gabapentin and carbamazepine. There were no differences in seizure-free rates.

Several important conclusions can be drawn from these studies. Older adults with epilepsy appear to be more responsive to treatment than younger adults. Seizure-free rates for all drugs were consistently greater than 50% in these studies compared with the 10% to 20% rates in most new AED studies. Adverse events seen with regular-release carbamazepine are reduced with extended-release dosage forms. In these studies, the AED doses needed to achieve optimal seizure control were lower than those typically used in younger patients. For example, the mean dose of lamotrigine in these studies ranged from 100 mg/day to 150 mg/day. Depending on the concomitant AED, lamotrigine doses are usually 150–200 mg/day with valproic acid and 300–500 mg/day in monotherapy or combined with enzyme-inducing AEDs. These conclusions are substantiated by a larger study that included carbamazepine, lamotrigine, oxcarbazepine, gabapentin, or topiramate and enrolled individuals of all age groups. When age was analyzed, individuals older than 65 years were more likely to become seizure free on whatever treatment they received.

Other AEDs have been studied in less elegant trials of the elderly. Ten AEDs were recently evaluated in a retrospective study design that included individuals older than 55 years. Lamotrigine had the highest retention and 12-month seizure-free rates compared with the other drugs; levetiracetam had the second-highest rates. Oxcarbazepine was consistently worse than all other drugs. An open-label study of topiramate in older adults suggested it was effective in controlling seizures, but the study lacked comparison with other AEDs.

Risk of Adverse Effects

Older adults with epilepsy are prone to higher rates of adverse events from AED pharmacotherapy. Data from the three major studies of AEDs show that older patients are more likely to discontinue an AED because of adverse events than because of lack of seizure control.

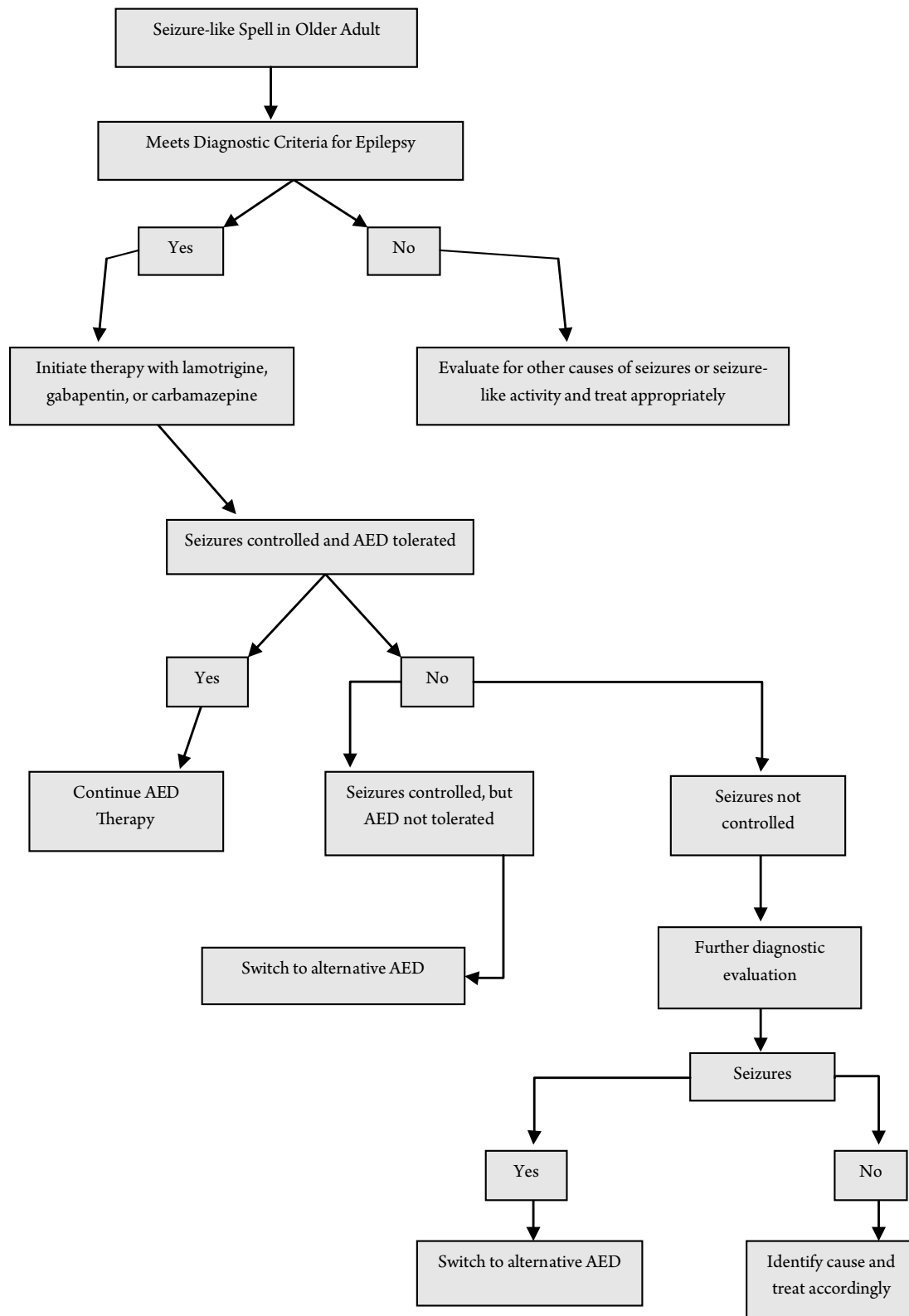


Figure 1-1. Treatment algorithm for new-onset seizures in older adults.

AED = antiepileptic drug.

The specific adverse events usually reported in these studies are listed in Table 1-1. In general, adverse events occurred in about 50% of patients. More than 40% of subjects who received regular-release carbamazepine discontinued treatment because of adverse events.

Because many of the adverse events in these studies affect a patient's function (e.g., cognition, falls), they must be carefully weighed when considering AED initiation in older adults. To minimize the risk of adverse events, AEDs must be carefully selected, matching common adverse events with patient characteristics. In addition, the occurrence of adverse events should be carefully monitored to rapidly detect and control those that might result in the discontinuation of an effective treatment. Patients and caregivers should be asked about adverse effects at every clinic visit, and the use of a standardized instrument such as the Adverse Events Profile should be encouraged.

AED Selection

Several factors must be considered when selecting an AED for the older adult. Care must be taken to ensure the following: the drug is appropriate for the seizure type, the adverse effect profile is compatible with the patient's characteristics, the unique pharmacokinetic properties of the AED are considered in light of the patient's comorbidities, and any drug interactions are avoided or managed. Without considering these factors, an improper drug may be selected, resulting in lack of efficacy or unnecessary harm to the patient.

Relationship to Seizure Type

In younger individuals, the efficacy of specific AEDs in treating certain seizure types is of great concern. Some AEDs can actually exacerbate seizures in younger adults (e.g., carbamazepine can worsen myoclonic seizures). However, this is not of great concern in older adults, because essentially, all new-onset seizures in this population are partial seizures. In studies of treatment of seizures in the elderly, the most common seizure type

Table 1-1. Incidence of Adverse Events in Older Patients Taking Carbamazepine, Gabapentin, or Lamotrigine Reported in Randomized, Prospective Studies

	Carbamazepine (% incidence)	Gabapentin (% incidence)	Lamotrigine (% incidence)
Neurologic Adverse Events			
Diplopia	8	9	7
Nystagmus	14	14	13
Dysarthria	9	12	9
Gait disturbance	29	29	27
Tremor	17	22	25
Sedation	6–51	46	2–40
Mood change	33	27	30
Cognitive difficulty	32	30	23
Dizziness	10–32	28	14–27
Headaches	11–18	15	11–19
Other Adverse Effects			
Rash/hypersensitivity	13–19	5	3–5
Weight gain > 18 lb	3	11	4
Weight loss > 4 lb	26	21	36
Water retention	9	20	10
Hyponatremia	11	4	7
Nausea/vomiting/diarrhea	2–32	24	3–34

Information from: Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomized comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. *Epilepsy Res* 1999;37:81–7; Rowan AJ, Ramsay RE, Collins JF, Pryor F, Boardman KD, Uthman BM, et al. New onset geriatric epilepsy, a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology* 2005;64:1868–73; and Saetre E, Perucca E, Isojärvi J, Gjesrstad L; LAM 40089 Study Group. An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. *Epilepsia* 2007;48:1292–302.

was complex partial seizures; also observed were generalized tonic-clonic, simple partial seizures, generalized tonic-clonic with partial seizures, and mixed partial seizures. Most seizures, even generalized tonic-clonic seizures, are considered partial seizures, not primarily generalized seizures. Therefore, essentially every available AED is considered efficacious. The only AED not indicated for partial seizures is ethosuximide. This highlights the importance of other factors when selecting an AED for an older adult.

Adverse Effect Profile and Patient Considerations

An AED often affects older adult patients with epilepsy much differently than younger individuals. For example, an individual with Parkinson disease may be especially prone to adverse effects on gait and balance and present with increased falls or tremor. Many AEDs will worsen memory and slow cognition, making them poor choices for individuals with even mild dementia. Weight gain is a common adverse effect of valproate, gabapentin, and pregabalin, and weight loss is common with topiramate and zonisamide. Changes in weight can be detrimental to the health of older adult patients, so caution must be exercised when selecting a drug that may affect weight.

Oxcarbazepine and carbamazepine can cause hyponatremia and generally should be avoided in patients who are sensitive to fluid and electrolyte imbalances or who are taking diuretics. Topiramate and zonisamide increase the risk of renal calculi and the development of metabolic acidosis. Finally, recent data have shown increased cardiovascular risk factors (e.g., lipid, homocysteine, C-reactive protein) in older individuals taking carbamazepine and phenytoin. Risk factors decrease when the phenytoin or carbamazepine is discontinued.

Another concern in older adults is depression, which occurs at a much higher incidence with diseases like Parkinson disease, stroke, and dementia. All AEDs carry warnings regarding depression and suicidality, and adding an AED may precipitate a major depressive episode. Depressive symptoms are more common with levetiracetam, topiramate, zonisamide, tiagabine, vigabatrin, and felbamate. Lamotrigine, oxcarbazepine, gabapentin, and pregabalin have lower rates of depression. With respect to self-harm and suicidal attempts, levetiracetam and, possibly, topiramate have a significantly higher incidence than other AEDs. Drugs with lower rates of depression and suicidality should be selected when caring for patients in whom there is a great risk of precipitating or exacerbating a major depressive episode.

When considering adverse effects as part of the drug selection process, the goal should be to avoid an AED with a high probability of decreasing the patient's ability to maintain a good quality of life or interfering with daily activity or overall function.

Pharmacokinetics

As people age, several physiologic changes occur that can alter the pharmacokinetic disposition of AEDs. However, few data document the clinical impact of these changes. In fact, recent data on the effects of aging on phenytoin, an AED previously associated with age-related changes in pharmacokinetics, indicate little if any difference between older adult and younger patients. The authors of this well-designed study concluded that age-related differences in phenytoin dosing are likely from increased sensitivity to the effects of the drug rather than pharmacokinetics.

Age-related decline in kidney function is well documented. Several newer AEDs (e.g., gabapentin, pregabalin, topiramate, zonisamide, lacosamide, levetiracetam) are completely or predominantly cleared by renal elimination. Kidney function should be monitored before initiating therapy with one of these AEDs and during ongoing treatment. Adjustments in doses/titration rates should be made in accordance with the manufacturer's recommendations to avoid unnecessary accumulation of drugs and potential adverse effects.

The prevalence of reduced gastric acidity increases with age, as does the potential for decreased absorption of weakly basic drugs and increased absorption of weakly acidic drugs. In addition, gastric emptying and gastrointestinal transit time are slowed and more variable in older patients. This variability in gastrointestinal physiology can result in unreliable absorption of sustained-release AED formulations and poor management of the patient's response. This explains the large variations in phenytoin trough concentrations seen in nursing home patients receiving consistent doses of phenytoin extended release.

Drug Interactions

Many AEDs, especially the older agents such as phenobarbital, phenytoin, carbamazepine, and valproate, have several drug interactions. This poses a problem in older adult patients, who are likely to be taking several drugs for chronic diseases. Patients in one study were taking an average of seven other medications. The importance and complexity of this issue were highlighted in a recent study of the incidence of interactions between AEDs and other drugs in older adults. The most common clinically important interactions were with cardiovascular drugs, agents for hyperlipidemia, analgesics, and anticoagulants. These interactions were found to potentially result in serious clinical adverse events for the patient.

Other classes of commonly used drugs that interact with AEDs include antidepressants (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors), antifungals, antiretrovirals, antineoplastics, antipsychotics, benzodiazepines, immunosuppressants, and steroids. The primary mechanism for most of these interactions involves cytochrome P450 (CYP) isoenzymes (Table

1-2). Although many interactions involve the induction or inhibition of CYP isoenzymes, other mechanisms (e.g., altered absorption) may also occur. For example, calcium-containing antacids, nutritional supplements, and tube feedings decrease phenytoin absorption.

Keys to managing or preventing AED drug interactions include the use of a single AED whenever possible for the control of seizures. Another strategy is to select a drug with a lower propensity for drug interactions. In general, newer AEDs (e.g., gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, zonisamide, pregabalin, lacosamide) have fewer drug interactions and tend to be easier to manage in older adult patients. Many of these AEDs are at least partially eliminated renally, reducing the possibility of drug interactions. Therapeutic drug monitoring (TDM) of AEDs may be helpful when serum concentrations are easily available and are related to therapeutic response. Finally, any change in the patient's treatment plan should result in closer monitoring of AED efficacy and adverse effects.

Pharmacotherapy Plan

An effective pharmacotherapy plan for older adult patients with epilepsy should include several elements including monitoring for efficacy and for adverse effects, adjusting doses appropriately, maintaining adherence,

and instructing patients or caregivers on what to do if a seizure occurs. These elements should be clearly communicated with the patient and other caregivers.

Appropriate Dosing

Typically, AEDs are initiated at low doses and gradually titrated to response. This approach minimizes the impact of dose-related adverse effects and allows more careful dosing, which balances efficacy and toxicity. Older adults typically respond at lower doses, and titration of doses to optimal response helps prevent overdosing.

Target doses for AEDs in older adults are often 50% to 75% of those in younger adults. Titration typically involves incremental increases on a weekly basis. The rate of increase depends on the drug involved. For example, lamotrigine has a strict protocol for therapy initiation because of the risk of serious rash, whereas other AEDs have more flexible titration options. Determining a reasonable target dose is based on several factors including kidney function for drugs with renal elimination, nutritional and albumin status for drugs with high protein binding, and liver function for drugs that are hepatically eliminated. Once the target dose is reached, patients are continually monitored to determine whether further dosage adjustments are needed to eliminate seizures or reduce dose-related adverse effects.

Table 1-2. Antiepileptic Drugs and CYP Enzymes

Drugs	CYP Substrates	CYP Inhibitors	CYP Inducers
Carbamazepine	2C8 (minor), 3A4 (major)		1A2, 2B6, 2C9, 2C19, 3A4, P-glycoprotein (all strong)
Ethosuximide	3A4 (major)		
Felbamate	2E1 (minor), 3A4 (major)	2C19 (weak)	3A4 (weak)
Oxcarbazepine	-	2C19 (weak)	3A4 (strong)
Phenobarbital	2C9 (minor), 2C19 (major), 2E1 (minor)		1A2 (strong), 2A6 (strong), 2B6 (strong), 2C8 (strong), 2C9 (strong), 3A4 (strong)
Phenytoin	2C9 (major), 2C19 (major), 3A4 (minor)		2B6 (strong), 2C8 (strong), 2C9 (strong), 2C19 (strong), 3A4 (strong)
Primidone			1A2 (strong), 2B6 (strong), 2C9 (strong), 3A4 (strong)
Tiagabine	3A4 (major)		
Topiramate		2C19 (weak)	3A4 (weak)
Valproic acid	2A6 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2E1 (minor)	2C9 (weak), 2C19 (weak), 2D6 (weak), 3A4 (weak)	2A6 (weak)
Zonisamide	2C19 (minor), 3A4 (major)		

CYP = cytochrome P450.

Efficacy Monitoring

The efficacy goal of pharmacotherapy in patients with epilepsy is the elimination of all seizures. Based on clinical trials of older adults, this goal should be easily achieved within 3–6 months of starting AEDs. However, in individuals who do not respond to the first two or three AEDs used in monotherapy, seizures are more difficult to control, or the individual may be having nonepileptic events. Video EEG monitoring should be attempted. If the patient is having epileptic seizures, a more reasonable goal may be to reduce the frequency of seizures. The only way to determine the efficacy of AED pharmacotherapy is to keep seizure calendars and counts of seizures. Electroencephalography and AED serum concentrations are unreliable markers of efficacy. Reliance on various tests or laboratory values as the sole determinant of efficacy is discouraged.

Of special interest to pharmacists is serum concentration monitoring. Although many pharmacists routinely use AED serum concentrations and TDM, no data show that routine TDM of AEDs improves patient outcomes. Serum concentrations of AEDs can be useful in benchmarking an optimal response, evaluating dose-related adverse effects, or checking adherence (Box 1-1). However, the interpretation of serum concentration data is complicated in older adults because of the large fluctuations that occur in serum concentrations even on stable doses of drug. In addition, weak correlations exist between serum concentrations and response for

older AEDs, and there are no established correlations for newer AEDs. For these reasons, every patient or caregiver should be given a seizure calendar or directed to use a Web site (e.g., www.seizuretracker.com, www.patientslikeme.com) to track seizures. Information on seizure counts should be available at each clinic visit.

Adverse Effect Monitoring

Dose-related adverse effects common to all AEDs in older adults include mental status changes, confusion, and sedation. Adjusting or reducing the dose will usually minimize or eliminate dose-related adverse effects. Chronic and idiosyncratic adverse effects also occur with AEDs. Chronic adverse effects occur months to years after therapy initiation. Idiosyncratic effects tend to be hypersensitivity reactions. Patients should be monitored at each clinic visit for these events. Ideally, a standardized tool like the Adverse Events Profile, a 19-item validated instrument for detecting AED adverse events, should be routinely used.

Recent studies have shown an association between AEDs and the development of osteopenia and osteoporosis. Contrary to previous impressions, essentially all AEDs have been shown to decrease bone mineral density as early as 6 months after treatment initiation. The precise mechanism for this effect is unclear, but for enzyme-inducing AEDs (i.e., phenobarbital, phenytoin, carbamazepine, and oxcarbazepine), it may be related to the induction of vitamin D metabolism. The risk of developing osteopenia and osteoporosis with AEDs is similar to that with corticosteroids. Current recommendations for individuals taking these drugs are to have vitamin D serum concentrations checked at least annually and bone mineral density checked at baseline and every 2–3 years thereafter. In addition, regular vitamin D and calcium supplementation are recommended. Calcium doses are usually 1200–2000 mg/day. Vitamin D doses are typically 800–2000 international units/day. However, precise doses have not been established.

As previously mentioned, all AEDs are associated with an increased risk of depression. Patients taking AEDs should be routinely monitored for depressive symptoms using one of the various tools (e.g., Beck Depression Inventory, Geriatric Depression Scale) for assessing mood. Should depression arise, the typical treatment is addition of an antidepressant, such as a selective serotonin reuptake inhibitor. Changing to an AED with less risk of depression (e.g., lamotrigine, gabapentin) is an option, but this could result in the return or worsening of seizures.

Idiosyncratic reactions are more common with AEDs than with other classes of drugs. Typically, these reactions occur during the first 6–12 months of therapy and are more common with the older AEDs. The most common idiosyncratic reactions are dermatologic, hepatic, and hematopoietic. Rashes are of great concern because

Box 1-1. Indications for AED Therapeutic Drug Monitoring

When targeting a specific serum concentration during initiation of treatment or a dose adjustment

To benchmark an optimal therapeutic response

To assist in determining magnitude of dose change (especially for phenytoin)

When there is difficulty in recognizing symptoms of concentration-related AED toxicity in patients (e.g., young children, developmentally delayed individuals, mentally incapacitated adults)

When there are persistent seizures with adequate AED doses

When drug interactions, altered pharmacotherapy regimen, or diseases can change AED pharmacokinetics

When monitoring changes in dosage form or substitution of generic products

When monitoring adherence

If there is an unexpected change in response to pharmacotherapy

AED = antiepileptic drug.

they can progress to Stevens-Johnson syndrome or toxic epidermal necrolysis. It is not possible to predict which rash will become severe; therefore, it is recommended that a patient discontinue the AED immediately on the first appearance of a rash. Medical attention should be obtained as soon as possible, and a new AED should be substituted.

Weight should be measured at each clinic visit, especially for AEDs known to alter body weight (e.g., valproate, gabapentin, pregabalin, topiramate, zonisamide). Serum sodium should be measured regularly in the older adult taking carbamazepine and oxcarbazepine because of increased risk of hyponatremia. Treatment of hyponatremia includes altering the AED dose, changing to another AED, increasing sodium intake, or implementing fluid restriction.

SPECIAL CONSIDERATIONS

Discontinuation of AEDs

A common dilemma in older patients is the question of discontinuing an AED when no seizures have been observed for a long period. It is prudent to consider this option because of the many detrimental adverse effects and multiple drug interactions encountered with AEDs. The criteria for discontinuing an AED include 2–5 years without documented seizures, a normal EEG, and the absence of any underlying pathology such as a tumor. If these criteria are met, the AED can be tapered over a 1- to 2-month period. Abrupt discontinuation may result in withdrawal seizures, confounding the attempt to discontinue the AED.

Seizure Prophylaxis

Trauma

Head injuries are relatively common events in older adults and, as in younger individuals, can precipitate epilepsy. Several studies have considered various drugs and regimens for the prevention of seizures after a moderate to severe head injury. The only effective preventive intervention in this instance is the use of phenytoin during the first week after the head injury. Other AEDs including valproate, carbamazepine, levetiracetam, and lamotrigine have been studied but have not been shown to be efficacious. In minor head injuries and after the first week of phenytoin prevention in moderate to severe head injuries, it is best to treat seizures if they occur. Ongoing prophylactic treatment with an AED may slow recovery from the injury and further impair cognitive function, which may be compromised by the injury.

Tumors

Seizures caused by primary brain tumors are quite common and should be treated when they occur. Selecting an AED is complicated by the need not to interfere with chemotherapy treatments for the tumor.

It has been thought that enzyme-inducing AEDs (e.g., phenytoin, carbamazepine, phenobarbital) would result in poorer chemotherapy outcomes. However, a study of AEDs in patients with glioblastoma shows that patients taking these drugs actually have better outcomes. The precise reason for this benefit is unknown. Care should still be taken to aggressively treat seizures in patients with tumors without altering response to chemotherapy.

Strokes

Seizures occur in about 50% of adults experiencing a stroke. Often, patients with severe strokes will present with status epilepticus, which is treated using the same protocols as in younger adults. The risk of seizures other than status epilepticus increases with factors such as cortical involvement, several lesions on neuroimaging, supratentorial lesions, old lesions on neuroimaging, family history of seizures, use of drugs known to cause seizures, large lesions, hemorrhagic lesions, and concurrent presence of cortical atrophy. At the first indication of seizure activity in a patient who has experienced a stroke, treatment with an AED should be initiated. Based on the previously described studies, lamotrigine or gabapentin is the preferred initial drug.

ROLE OF THE PHARMACIST

Data show that access to primary care is a major determinant of optimal outcomes in older adult patients with epilepsy. Pharmacists play an instrumental role in providing access to this care. Several functions performed by a pharmacist are vital to improving the care of older adult patients with epilepsy. These include assisting in the selection of the correct AED, monitoring efficacy and toxicity, managing various aspects of AED therapy (e.g., drug interactions, pharmacokinetic changes), and assisting patients and caregivers with issues related to adherence.

Pharmacists also play a key role in advising patients on the selection of over-the-counter medications and herbal products. Recommendations for these products must include a consideration of possible drug interactions with AEDs; for example, cimetidine and omeprazole can increase serum concentrations of phenytoin and carbamazepine, respectively. In addition, certain products (e.g., decongestants, ginkgo biloba) have been reported to cause or increase seizures. In several major epilepsy centers, pharmacists are integral to the delivery of care to patients with epilepsy. To receive the highest level of recognition by the National Association of Epilepsy Centers, a pharmacist must be involved in the clinical activities of the center.

A survey of patients with epilepsy showed that patients with epilepsy, although not fully using their

pharmacist in assisting in AED management, desire the increased involvement of their pharmacist in the care of their epilepsy. However, more elaborate studies on the impact of pharmacists in the care of patients are lacking. Without these pharmacist activities, the care of older adult patients with epilepsy is compromised, and poor seizure control or unwanted adverse effects are likely.

ANNOTATED BIBLIOGRAPHY

1. Scarmeas N, Honig LS, Choi H, Cantero J, Brandt J, Blacker D, et al. Seizures in Alzheimer disease: who, when, and how common? *Arch Neurol* 2009;66:992–7.

This prospective observation study describes the incidence and potential predictors of new-onset seizures in 453 patients with Alzheimer disease. Caregivers were interviewed to determine whether a seizure might have occurred and whether a diagnosis or treatment was made. For those who screened positively to one of those questions, two epileptologists reviewed the medical records for evidence supporting caregiver reports. Fifty-two of 453 patients (11.5%) screened positively for possible new-onset seizures. The study epileptologists determined that seven (13%) had epileptic events, which is about 1.5% of the total study population. Younger patients (mean age 70.7 years) had a higher risk of seizures (odds ratio [OR] 1.23; 95% confidence interval [CI], 1.08–1.41; $p=0.003$). Although this study provides a realistic estimate of seizure incidence in Alzheimer disease, it is limited by its dependence on caregiver reports of seizures and retrospective analysis of data by physicians to make a seizure diagnosis.

2. Pugh MJ, VanCott AC, Steinman MA, Steinman MA, Mortensen EM, Amuan ME, et al. Choice of initial antiepileptic drug for older veterans: possible pharmacokinetic drug interactions with existing medications. *J Am Geriatr Soc* 2010;58:465–71.

A cohort of 9682 older veterans meeting criteria for new-onset epilepsy were identified from national VA and Medicare data from October 1, 1999, to September 30, 2004. Clinically meaningful drug interactions, defined as interactions that might affect the clinical management of the patient or that might have severe adverse outcomes for patients, were identified in these patients. Primary comorbidities in this group included hypertension (87.0%), hypercholesterolemia (58.2%), cerebrovascular disease (57.2%), heart disease (46.2%), chronic obstructive pulmonary disease (44.8%), diabetes mellitus (38.5%), cardiac arrhythmias (37.8%), dementia (25.2%), other neurologic conditions (17.4%), and kidney failure (12.9%). The investigators determined that 60.1% of study subjects had at least one potential clinically important drug interaction with the initial AED. Around 45% of patients received a refill of the potentially interacting drug. Percentages of AEDs potentially interacting with other AEDs were phenytoin (57.5%), phenobarbital (51.6%), carbamazepine (55.5%), and valproate (17%). Other drugs that interacted with AEDs included cardiovascular drugs

(26.4%), lipid-lowering drugs (20.7%), psychotropic drugs (14.9%), and anticoagulants (6.2%). The strongest predictors of a clinically important drug interaction included AEDs initiated in the emergency department (OR 1.30; 99% CI, 1.08–1.58; $p<0.001$) or in primary care (OR 1.29; 99% CI, 1.12–1.49; $p<0.001$) and clinical characteristics such as cerebrovascular disease (OR 1.22; 99% CI, 1.08–1.36; $p<0.001$), hypertension (OR 1.46; 99% CI, 1.24–1.82; $p<0.001$), or hypercholesterolemia (OR 1.40; 99% CI, 1.24–1.57; $p<0.001$). Individuals receiving six or more drugs also had a greater risk of a clinically important drug interaction (OR 1.36; 99% CI, 1.20–1.55; $p<0.001$). This study shows the magnitude of the problem with interactions between AEDs and other drugs in older adults. However, it does not document the clinical impact of these interactions on patient outcomes or describe ways of managing the interaction.

3. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs – best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia* 2008;49:1239–76.

This position paper was prepared by an international panel of epilepsy experts to outline the rationale for monitoring serum concentrations of AEDs and to describe the relationships of serum drug concentrations to pharmacokinetics, potential drug interactions, efficacy, and clinical circumstances in which TDM might be of particular benefit. Based on published evidence, the panel found that routine TDM has not proved beneficial in improving control of seizures or patient outcomes. For highly protein-bound drugs (e.g., phenytoin, valproate, tiagabine), TDM is warranted when alteration in protein binding is suspected. Examples of these situations include pregnancy, old age, neonatal status, liver disease, and kidney disease. Specific recommendations for each AED are provided. For example, carbamazepine concentrations may be useful in detecting and managing potential drug interactions. If concentrations are measured, it is recommended that samples be drawn before the first dose of the day. Finally, the panel recommends when TDM may be useful and provides guidelines for the appropriate use of serum concentration in TDM. Although this article describes expert opinion, the conclusions of the panel are based on published evidence for the TDM of AEDs. Guidelines from this report should be incorporated into protocols for AED TDM.

4. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomized comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. *Epilepsia Res* 1999;37:81–7.

This is one of only three head-to-head, prospective, randomized, blinded studies evaluating the efficacy of AEDs in the treatment of new-onset seizures in the elderly. In this study, 150 patients older than 65 years were randomized in a 2:1 ratio to lamotrigine or

immediate-release carbamazepine. To be enrolled in the study, patients had to have experienced at least two seizures in the previous year that met diagnostic criteria for epilepsy. Doses were titrated to a target of 100 mg/day for lamotrigine and 400 mg/day for carbamazepine. Once target doses were achieved, additional dose adjustments were allowed on the basis of control of seizures or occurrence of dose-related adverse effects. Patients were observed for 24 weeks after starting an AED. Major outcome measures were the number of patients who withdrew early from the study and the proportion of patients who were seizure free for the last 16 weeks of the study. At study conclusion, patients who completed the study were receiving a median of 100 mg/day of lamotrigine and 400 mg/day of carbamazepine. Significantly more patients receiving lamotrigine (71%) than patients receiving carbamazepine (42%) remained in the study. There were no differences in the number of patients becoming seizure free on either drug, with a wide CI indicating the study had a low power to detect a difference in this outcome. The difference in withdrawal rate was caused by a significant difference ($p < 0.001$) in adverse effects, with lamotrigine having fewer adverse effects than carbamazepine. In addition to the difference in withdrawal rates, this study highlights the responsiveness and sensitivity of older adults to AEDs, as indicated by the relatively low doses of lamotrigine and carbamazepine, the rather large seizure-free rates observed, and the incidence of adverse events with both drugs.

5. Rowan AJ, Ramsay RE, Collins JF, Pryor F, Boardman KD, Uthman BM, et al. New onset geriatric epilepsy, a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology* 2005;64:1868–73.

In this randomized, double-blind study, gabapentin, lamotrigine, and carbamazepine were compared in adults older than 60 years with new-onset epilepsy. With 593 patients enrolled and observed for a full year, this was the largest and most prolonged study of the pharmacotherapy of epilepsy in older adults. To enter the study, patients had to have experienced at least one seizure in the previous 3 months and had to have received either no prior AED treatment, less than 1 month of AED treatment, or subtherapeutic treatment with an AED. The primary outcome measure was retention in the study 12 months after randomization. Secondary outcomes included being seizure free at 12 months, time to the first seizure after starting the study, and adverse effects of AEDs. A power analysis showed the need for 720 participants to detect a 15% difference between treatment groups in the primary outcome, with the assumption of a 65% overall retention rate. The initial target doses were 1500 mg/day for gabapentin, 150 mg/day for lamotrigine, and 600 mg/day for carbamazepine. After titration to the target doses, further adjustments were permitted to control seizures or limit adverse events. Mean doses at the end of the study were gabapentin 1422 mg/day, lamotrigine 152 mg/day, and carbamazepine 582 mg/day. Significantly more patients terminated carbamazepine early compared with either

gabapentin or lamotrigine, and significantly fewer patients receiving lamotrigine withdrew because of adverse effects than patients taking gabapentin or carbamazepine. Differences in responses were seen as early as weeks 4–5. Individuals who terminated the study early had a mean age of 73 years compared with the mean age of 71.5 years for those completing the study ($p = 0.0193$). Seizure-free rates were almost identical for all three treatments, as were the times to first seizure. Occurrence of adverse events accounted for essentially all early terminations. Seven serious hypersensitivity reactions that required hospitalization occurred, with six of these patients being in the carbamazepine group. One patient in the carbamazepine group died after a hypersensitivity reaction. The average number of concomitant drugs for individuals in this study was seven, showing the increased possibility of interactions. Results of this study validate those of the earlier study comparing lamotrigine and carbamazepine. From these data, it appears that the chances of having to discontinue AED treatment because of adverse effects increases with age.

6. Saetre E, Perucca E, Isojärvi J, Gjesrstad L; LAM 40089 Study Group. An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. *Epilepsia* 2007;48:1292–302.

This study attempted to determine whether some of the previously noted problems with immediate-release carbamazepine in older adults could be alleviated by the use of sustained-release carbamazepine. Patients enrolled in the study were older than 65 years and had experienced at least two unprovoked seizures in the previous 6 months. Doses of lamotrigine were titrated to a maximum of 500 mg/day, and for carbamazepine, 2000 mg/day. The primary outcome was retention in the study for 36 weeks after starting the assigned treatment. Secondary end points included being seizure free, time to first seizure after starting treatment, adverse effects, and tolerability as measured by the adverse event profile. A power analysis determined that 190 patients were needed to detect a 20% difference between the treatment groups. Some 186 patients were enrolled. The mean dose of lamotrigine at the end of the study was 117 mg/day, and the mean dose of carbamazepine was 419 mg/day. Seventy-three percent of patients taking lamotrigine and 67% of patients taking carbamazepine completed the study. There was no significant difference in seizure-free rates, time to first seizure, or tolerability evaluation. Although not a direct comparison of immediate-release carbamazepine to sustained-release carbamazepine, this study appears to indicate that at least some of the problems with carbamazepine noted in the other studies of older adults are overcome using a sustained-release formulation. This study also substantiates the observations in the two previous studies that older adults are responsive and sensitive to AED treatment, given the rather high lamotrigine and

carbamazepine seizure-freedom rates (greater than 40%) and the rather low doses used.

7. Ahn JE, Cloyd JC, Brundage RC, Marino SE, Conway JM, Ramsay RE, et al. Phenytoin half-life and clearance during maintenance therapy in adults and elderly patients with epilepsy. *Neurology* 2008;71:38–43.

Phenytoin is commonly prescribed in the elderly, but it is not recommended by most epileptologists because of its adverse effects. Although there have been many reports of age-related changes in phenytoin pharmacokinetics, this study attempted to address weaknesses and conflicting results from previous studies. Using a stable-labeled phenytoin isotope that allowed the administration of a regular maintenance dose of phenytoin, this study attempted to identify differences in phenytoin metabolism caused by age or sex. Older adults (i.e., 65 years or older) taking phenytoin were enrolled at a 2:1 ratio with younger adults also taking phenytoin. Patients receiving drugs known to interact with phenytoin were excluded. While maintaining their maintenance phenytoin dose, subjects received a 100-mg intravenous dose of stable-labeled phenytoin or 100 mg of a phenytoin-equivalent dose of stable-labeled fosphenytoin. Sixty-two subjects had 70 pharmacokinetic studies completed using the stable-labeled isotope. After the NONMEM analysis of data from the stable-labeled isotope studies, no age or sex differences were found in clearance, volume of distribution, or half-life. A separate analysis of maintenance doses showed that mean phenytoin doses were 4.3 mg/kg/day in older adults and 5.5 mg/kg/day in younger adults, a significant difference. Unbound phenytoin concentrations were similar between younger and older individuals and between men and women. The mean half-life for all groups was about 40 hours, which is 2–6 times longer than previously reported. Many of the differences in findings between this study and previously reported studies may be attributable to the evaluation of pharmacokinetic parameters in patients receiving a stable maintenance dose of phenytoin and the greater data precision afforded by the use of a stable-labeled isotope. Results from this study indicate that phenytoin doses should only be changed after sufficient time to ensure steady state has transpired. In addition, with the prolonged half-life documented in this study, it is possible to use once-daily dosing of phenytoin, regardless of which dosage form is used.

8. Gilliam FG, Fessler AJ, Baker G, Vahle V, Carter J, Attarian H. Systematic screening allows reduction of adverse antiepileptic drug effects, a randomized trial. *Neurology* 2004;62:23–7.

Although not performed solely in older adults, this study emphasizes the importance of carefully screening patients with epilepsy for the adverse effects of AEDs. Patients from a single epilepsy center were initially screened for AED toxicity using the validated Adverse Events Profile. When a patient had a score in the toxicity range, the individual was randomized to have results of the Adverse Events Profile available to the treating

physician or not. Patients were observed for 4 months, and the Adverse Events Profile was readministered at the end of this period. The primary outcome was a difference in the total Adverse Events Profile score between the first and last assessment. In addition, patients completed the Quality of Life in Epilepsy-89 instrument, the values of which were used as a secondary outcome measure. Other outcome measures included number of clinic visits, number of dose changes, and seizure frequency. Sixty-two of 200 patients screened were determined to be toxic by the Adverse Events Profile and were randomized to one of the two groups. The mean improvement in the Adverse Events Profile score was significantly greater in the patients whose physician had access to the results of the profile ($p=0.01$). There was no difference between the groups in the mean change of the Quality of Life in Epilepsy-89 scores. However, for patients in whom the Adverse Events Profile score was available to the physician, there were significantly fewer clinic visits, fewer dose or drug changes, and lower seizure frequency. An instrument like the Adverse Events Profile should be used at each clinic visit, and the results should be made available to the physicians and pharmacists responsible for managing the patient's AED therapy.

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The use of AEDs in epilepsy and the risk of self-harm or suicidal behavior are especially important issues for older adults because many of the etiologies of epilepsy in this age group (e.g., stroke, dementia, neurotrauma) also involve depression. In this nested, case-control study of 44,300 patients with epilepsy, the authors explore possible differences between AEDs in reports of self-injurious or suicidal behavior. Age was not included as criteria for inclusion. The authors accessed the United Kingdom General Practice Research Database for this study. Patients who received at least one prescription for an AED and a confirmed diagnosis of epilepsy or non-febrile seizures between January 1, 1990, and September 30, 2005, were eligible for inclusion. Records were reviewed for the first report of self-harm or suicidal behavior, death, termination with a particular medical practice, or end of the study. Antiepileptic drugs were classified as barbiturates, conventional AEDs (e.g., carbamazepine, valproate, phenytoin, ethosuximide, acetazolamide), new AEDs with a low risk of depression (e.g., oxcarbazepine, lamotrigine, gabapentin, pregabalin), and new AEDs with a high risk of depression (e.g., levetiracetam, tiagabine, topiramate, vigabatrin). The authors identified 453 cases with reports of self-harm or suicidal ideation and included them in the analysis. A control cohort of 20 individuals for every case was also identified for comparison. Use of new AEDs with a high risk of depression was associated with an almost 3-fold increased risk of self-harm or suicide attempts compared with newer AEDs with a low risk of depression. Other AEDs were not associated with an increased risk. When specific drugs were analyzed, the risk of self-harm

and suicidal behavior strongly correlated with levetiracetam use. On the basis of these findings, using levetiracetam in older adults who are at an increased risk of depression may not be advisable.

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Because AED pharmacotherapy is the mainstay of treating epilepsy in older adults, these investigators studied the frequency of clinic visits and epilepsy outcomes using the Western Australia Data Linkage System. Data for patients older than 65 years from January 1, 1992, to December 31, 2006, were extracted from several databases in this system. A total of 3527 patients with epilepsy met all the inclusion criteria for the study. Patients were observed for an average of 11.5 years, with an all-cause mortality rate of 91.1 deaths per 100,000 person-years. There was a statistically significant inverse relationship between the number of primary care clinic visits and mortality rates ($p=0.0005$). A secondary outcome measure, hospitalization caused by epilepsy, did not differ in relation to the number of clinic visits. Access to primary care appears to be a main determinant in the mortality rates of older patients with epilepsy. It may be possible to carry over the results of this study to the provision of care by pharmacists in monitoring and managing AED therapy in older adults.

11. Birnbaum AK. Pharmacokinetics of antiepileptic drugs in elderly nursing home residents. *Int Rev Neurobiol* 2007;81:211–20.

This review summarizes several important findings from studies of AED use among nursing home residents. Around 45% of nursing home residents taking phenytoin have serum concentrations below the typical reference range, and 10% have concentrations above the range. Phenytoin serum concentrations vary as much as 200% within an individual resident from one measurement to the next. This is despite excellent adherence and consistency in timing of blood draws for serum concentrations. Valproate is used by about 15% of nursing home residents, but most valproate use is not for an epilepsy indication. Average valproate doses decline in individuals older than 85 years. Carbamazepine is also commonly used at mean doses of 8.8 mg/kg/day and mean serum concentrations of 6.3 mg/L. Around 20% of carbamazepine serum concentration measurements were judged to be subtherapeutic. A common combination is phenobarbital and phenytoin, which is potentially harmful because both drugs produce sedation and impaired cognition. Gabapentin is often prescribed, but caution should be used in dosing the drug in patients with declining kidney function. The large variability in serum concentrations makes AED management in this group of patients extremely difficult and calls for close monitoring of efficacy and adverse effects.

12. Arana A, Wentworth CE, Ayuso-Mateos JL, Arellano FM. Suicide-related events in patients treated with antiepileptic drugs. *N Engl J Med* 2010;363:542–51.

Suicidality, suicidal ideation, or suicidal behavior is a concern with AEDs that has received much recent attention. Although not performed solely in older adults, this epidemiologic study attempted to determine the association between AEDs and suicide-related events in the United Kingdom. Using the Health Improvement Network database, which includes 6.7 million patients, the authors screened for several cohorts. These cohorts included patients without epilepsy, depression, or bipolar disorder and not taking AEDs; patients with epilepsy not taking AEDs; patients with epilepsy taking AEDs; patients with depression not taking AEDs; patients with depression taking AEDs; patients with bipolar disorder not taking AEDs; patients with bipolar disorder taking AEDs; patients with epilepsy and depression not taking AEDs; patients with epilepsy and depression taking AEDs; patients with epilepsy and bipolar disorder not taking AEDs; and patients with epilepsy and bipolar disorder taking AEDs. The authors attempted to identify five controls for each case that were matched according to age, sex, and clinical practice. A crude incidence of suicide-related events was calculated among the case cohorts, and a case-control analysis was done to determine the association between the use or nonuse of AEDs and suicidal events. The total patients included 5,130,795 patients in the cohorts and 4,514,366 patients in the control group. The incidence of suicide-related events among patients without epilepsy, depression, or bipolar disorder and not taking AEDs was 15.0/100,000 person-years (95% CI, 14.6–15.5). For individuals with epilepsy and not taking AEDs, the incidence more than doubled at 38.22/100,000 person-years (95% CI, 26.3–53.7) and was even greater in patients with epilepsy taking AEDs at 48.2/100,000 person-years (95% CI, 39.4–58.5). In patients with depression not taking AEDs, the incidence was 129.1/100,000 person-years (95% CI, 124.7–133.6), and the incidence was 177.3/100,000 patient-years (95% CI, 155.2–201.6) for patients with depression taking AEDs. Several other important comparisons are made in this study. Individuals with epilepsy have an increased incidence of suicide-related events, and AEDs further increase the risk. The study did not break down the risk by AED to determine whether the increased incidence was caused by specific AEDs. However, the study highlights the importance of monitoring for depression and suicidality in all individuals with epilepsy or taking AEDs.

13. Leone MA, Tonini MC, Boglium G, Gionco M, Tassinari T, Bottacchi E, et al. Risk factors for a first epileptic seizure after stroke. A case control study. *J Neurol Sci* 2009;277:138–42.

As noted from epidemiologic studies, strokes are the most common cause of new-onset epilepsy in older adults. A group of 725 patients who presented with a first seizure were assessed to determine whether the seizures were idiopathic/cryptogenic or symptomatic. From these patients, 385 were identified as having symptomatic seizures, with 324 of these considered to have seizures caused by stroke, head trauma, or brain tumor. Of symptomatic patients, 293 were

evaluable, with 161 falling into the stroke diagnosis. Of these stroke patients, 105 had seizures acutely caused by stroke, and 56 had remote strokes (i.e., new-onset seizures with only computerized tomography [CT] evidence of a previous stroke). Control subjects who experienced a stroke but who did not have seizures were identified and matched for age, sex, and location of the stroke. A multivariate analysis identified three predictors of new-onset seizures as cortical involvement (OR 3.3; 95% CI, 2.1–5.0), prior lesions on CT scan (OR 2.2; 95% CI, 1.4–3.4), and hemorrhagic lesions (OR 1.8; 95% CI, 1.0–3.2). There was a sex difference in independent predictors of seizures. For women, the predictors were cortical involvement and prior lesions on CT scan. For men, the predictors were cortical involvement and family history of seizures. Multivariate analysis of remote symptomatic seizures showed the significant predictors to be cortical involvement (OR 3.8; 95% CI, 1.7–8.4), large size (OR 3.6; 95% CI, 1.1–11.5), and prior lesions on CT scan (OR 2.7; 95% CI, 1.2–6.0). For acute symptomatic seizures, the significant predictors were cortical involvement (OR 3.8; 95% CI, 2.1–6.6), average daily intake of alcohol of more than 50 g/day (OR 3.5; 95% CI, 1.5–8.0), hemorrhagic stroke (OR 2.3; 95% CI, 1.1–4.5), and prior lesions (OR 2.1; 95% CI, 1.2–3.9). It appears that the most consistent predictors of seizures are cortical involvement, large lesions, and hemorrhagic strokes. Alcohol consumption may have an important role in new-onset seizures after acute stroke, and there may be sex differences in predictors of seizures caused by strokes. Individuals with these predictors should be monitored very closely for seizures, and an appropriate AED should be initiated after the first seizure.

14. Arif H, Buchsbaum R, Pierro H, Whalen M, Sims J, Resor SR, et al. Comparative effectiveness of 10 antiepileptic drugs in older adults with epilepsy. *Arch Neurol* 2010;67:408–15.

Prospective comparative studies between AEDs of the elderly are limited. These authors attempted to provide comparative data on several AEDs through a retrospective comparative effectiveness study. Using the database, which spanned 2000–2005, of a single comprehensive epilepsy center, 470 patients with epilepsy and older than 55 years were identified. The percentage of patients remaining who were taking an AED and the rates of seizure freedom were the primary outcomes. Ten different AEDs were taken by at least 10 patients and were included in the analysis. Seventy-nine percent of patients starting on lamotrigine remained on the drug at 12 months after initiation; for levetiracetam, this number was 73%. Lamotrigine retention was significantly higher than that for phenytoin (59%), gabapentin (59%), topiramate (56%), carbamazepine (48%), and oxcarbazepine (24%). Levetiracetam retention was significantly higher than that for carbamazepine and oxcarbazepine. Seizure-freedom rates were 54% for lamotrigine and 43% for levetiracetam, and seizure-free rates for all other AEDs were below 30%. Stratification for refractory or non-refractory epilepsy, being seizure free, and retention did not alter these findings. The most

common adverse effects that resulted in discontinuation or dose changes of an AED were imbalance, drowsiness, and gastrointestinal problems. These data are generated from a retrospective study at a single center, resulting in several potential problems with bias in drug selection and use. However, they suggest that lamotrigine and levetiracetam are better tolerated and have slightly higher seizure-free rates than other AEDs. In addition, oxcarbazepine consistently performed worse in this age group compared with all other AEDs.

15. McAuley JW, Miller MA, Klatter E, Shneker BF. Patients with epilepsy's perception on community pharmacist's current and potential role in their care. *Epilepsy Behav* 2009;14:141–5.

In this study, 75 adult patients with epilepsy were surveyed regarding their perceptions and opinions about the care they receive from community pharmacists. Most patients sought information from pharmacists for information on drug interactions and adverse effects of AEDs. At much lower rates, patients worked with pharmacists in monitoring seizure frequency, adhering to AEDs, maintaining a medication profile, and discussing the impact of epilepsy on lifestyle. Most patients wanted their pharmacist to effectively communicate with their physician regarding drug interactions and adverse reactions. Patients reported good relationships with their pharmacists, but they expressed concerns about confidentiality when talking with their pharmacist and a hesitancy to pay for additional services. The results of this survey provide insights into ways that pharmacists can provide additional care to patients with epilepsy and improve the care they receive.

SELF-ASSESSMENT QUESTIONS

Questions 1–3 pertain to the following case.

P.B. is a 71-year-old woman (weight 68 kg) who has developed spells in which she loses consciousness and has movements of her mouth. These episodes last for less than 1 minute and occur several times a week. She has atrial fibrillation. Current drugs include warfarin dose adjusted to maintain an international normalized ratio (INR) of 2–3, lisinopril 5 mg/day, and hydrochlorothiazide 25 mg/day. P.B.'s vital signs, laboratory values, and other test results are as follows: blood pressure 135/85 mm Hg; heart rate 82 beats/minute; sodium 138 mEq/L; potassium 4.0 mEq/L; chloride 102 mEq/L; carbon dioxide 23 mEq/L; serum creatinine 1 mg/dL; blood urea nitrogen 12 mg/dL; and INR 2.3. A magnetic resonance imaging scan of her head shows several white matter lesions; electroencephalography (EEG) shows mild generalized slowing with no epileptiform activity.

1. **Which one of the following seizure types is P.B. most likely experiencing?**
 - A. Generalized tonic-clonic.
 - B. Absence.
 - C. Myoclonic.
 - D. Complex partial.
2. **Which one of the following antiepileptic drugs (AEDs) would be best for P.B.?**
 - A. Carbamazepine.
 - B. Lamotrigine.
 - C. Oxcarbazepine.
 - D. Phenytoin.
3. P.B. receives appropriate treatment for her seizures and goes for 3 years without a documented seizure. Medically, she remains relatively stable, except for a new diagnosis of hypercholesterolemia, for which she is initiated on atorvastatin 40 mg/day. A repeat EEG is read as normal, and her magnetic resonance image of the brain is essentially unchanged. She is not experiencing any known adverse effects to her drug. **Which one of the following options is the best approach to managing P.B.'s AED at this point?**
 - A. Gradually taper over 1 month.
 - B. Continue the drug unchanged.
 - C. Reduce the dose by 50%.
 - D. Increase the dose by 25%.

Questions 4–8 pertain to the following case.

F.G. is a 67-year-old man with a history of myocardial infarction, depression, mild dementia, and hypertension. His current drugs include metoprolol, donepezil,

sertraline, and lisinopril. His blood pressure is 125/84 mm Hg, heart rate is 79 beats/minute, Geriatric Depression Scale score is 2, and Mini-Mental State Examination score is 20. Recently, F.G. has been experiencing several episodes of abrupt and brief forgetfulness. His wife has observed his right hand fumbling with his clothes during these spells.

4. **Which one of the following is the most likely cause of F.G.'s spells?**
 - A. Cerebrovascular disease.
 - B. Cardiac arrhythmia.
 - C. Dementia.
 - D. Syncope.
5. The physician suspects F.G.'s spells are seizures. **Which one of the following options is the best approach to F.G.'s treatment?**
 - A. Order EEG to determine whether these spells are seizures.
 - B. Initiate an AED to help with his depression and dementia.
 - C. Do not initiate an AED because the risk of adverse events outweighs the risk of recurrence.
 - D. Initiate an AED because these spells are epilepsy.
6. After completing the workup, F.G.'s physician wishes to initiate carbamazepine. **Which one of the following dosing schemes is best?**
 - A. Titrate carbamazepine to 400 mg three times/day over 1 month.
 - B. Titrate carbamazepine to a serum concentration target of 4–12 mcg/mL.
 - C. Titrate carbamazepine to 300 mg two times/day over 1 month.
 - D. Titrate carbamazepine to a serum concentration target of 10–15 mcg/mL.
7. F.G. is initiated on the appropriate dose of carbamazepine. **Which one of the following would be best to monitor when initiating this treatment in F.G.?**
 - A. Vitamin D concentrations.
 - B. Potassium.
 - C. INR.
 - D. Serum creatinine.
8. Two months after starting carbamazepine, F.G.'s blood pressure is 155/92 mm Hg, heart rate is 98

beats/minute, Geriatric Depression Scale score is 1, and Mini-Mental State Examination score is unchanged. **Which one of the following drugs would be best to increase in F.G.?**

- A. Lisinopril.
- B. Metoprolol.
- C. Donepezil.
- D. Sertraline.

9. A 74-year-old woman suffered an ischemic stroke 6 months ago. In the past month, she has experienced three spells consistent with seizures. Her current drugs include clopidogrel, hydrochlorothiazide, simvastatin, and citalopram. Because of concerns about drug interactions, her physician chooses to initiate levetiracetam for her seizures. **Which one of the following would be best to monitor in this patient at each clinic visit because of starting levetiracetam?**

- A. Mini-Mental State Examination.
- B. Beck Depression Inventory.
- C. Hamilton Anxiety Rating Scale.
- D. Alzheimer Disease Assessment Scale-Cognitive.

10. A 75-year-old woman suffered a stroke 3 months ago that involved the left hemisphere of the brain. For the past 2 months, she has experienced episodes of sudden, brief behavior changes associated with twitching of the right side of her face. In addition, she has developed shingles and is suffering from postherpetic neuralgia. Her other medical problems include hypertension that is controlled with valsartan, diabetes that is controlled with metformin, and mild depression that is treated with sertraline. Because of severe neuralgic pain, she is initiated on gabapentin, and her sertraline is changed to duloxetine. Lamotrigine is initiated for treatment of the episodes of behavior change and facial twitching. One month later, she develops a pruritic rash that starts on her chest and abdomen. **Which one of the following is the best approach to managing this patient's rash?**

- A. Discontinue gabapentin.
- B. Discontinue lamotrigine.
- C. Discontinue valsartan.
- D. Discontinue duloxetine.

11. A 72-year-old man with Parkinson disease and atrial fibrillation fell 2 days ago, hitting his head on concrete and experiencing a loss of consciousness. He was immediately transported to the emergency department, where it was determined that he had a large, acute, subdural hematoma. He was treated by

neurosurgery with burr holes and evacuation of the clot within several hours of the injury. Currently, he is oriented to person and responds slowly to painful stimuli. His home drugs before admission included warfarin and ropinirole. Because of concerns about seizures, phenytoin was initiated immediately after surgery. **Which one of the following is the best approach to AED use in this patient?**

- A. Change phenytoin to levetiracetam.
- B. Continue phenytoin for 2 years after his surgery.
- C. Discontinue phenytoin immediately.
- D. Continue phenytoin for 7 days after surgery and then stop.

12. A 78-year-old nursing home resident is receiving phenytoin chewable tablets 300 mg once daily for seizures. Her recent phenytoin serum concentration, measured about 2 hours after a dose, was 25 mg/L. Two months ago, her phenytoin serum concentration, measured about 3 hours before a dose, was 8 mg/L on the same phenytoin dose. The physician is concerned about the most recent concentration. She has not had documented seizures during the past year, and she does not appear to be having adverse effects. **Which one of the following options would be best for this patient?**

- A. Audit patient adherence.
- B. Decrease the phenytoin dose to 250 mg/day.
- C. Continue the current phenytoin dose.
- D. Change the phenytoin dose to 150 mg twice daily.

13. An 80-year-old man has taken carbamazepine for 3 years for epilepsy. He also takes atorvastatin for hypercholesterolemia, aspirin for prevention of cardiovascular events, and hydrochlorothiazide for hypertension. At this visit, he is experiencing dizziness and fatigue. For the past three clinic visits, his serum sodium concentration has been less than 128 mEq/L. His carbamazepine serum concentration is 5 mg/L. His physician decides to change carbamazepine to another AED. **Which one of the following options would be best for this patient?**

- A. Gabapentin.
- B. Oxcarbazepine.
- C. Phenytoin.
- D. Ethosuximide.

14. A 68-year-old man is initiated on lamotrigine for episodes that appear to be seizures. He is also being treated with warfarin for atrial fibrillation, metoprolol for hypertension, and famotidine for gastric reflux. **Which one of the following is most**

important to monitor at each clinic visit because the patient started taking lamotrigine?

- A. Adverse Events Profile.
- B. Beck Depression Inventory.
- C. INR.
- D. Mini-Mental State Examination.

15. An 82-year-old woman has been in a nursing home for 10 years after an apparent stroke. She has been in the current facility for 3 months. Her drugs consist of phenytoin, metoprolol, aspirin, and simvastatin. Her family and nursing home staff report that she is ataxic and drowsy. Her EEG shows mild to moderate generalized slowing. Neuroimaging shows no major lesions. Records from her current and previous facility indicate no observed seizures for at least 2 years. **Which one of the following options would be best for this patient?**

- A. Switch to lamotrigine.
- B. Switch to gabapentin.
- C. Discontinue phenytoin immediately.
- D. Taper off phenytoin.

16. A 68-year-old woman is taking atorvastatin 20 mg/day for hypercholesterolemia, aspirin 81 mg/day for transient ischemic attack, and lisinopril 10 mg/day for hypertension. She recently received a diagnosis of epilepsy and was initiated on carbamazepine sustained release. Her other disorders are well controlled. **Which one of the following is most important to monitor in this patient?**

- A. Platelet count.
- B. Blood pressure.
- C. Lipid profile.
- D. Serum creatinine and blood urea nitrogen.

17. A 72-year-old man is initiated on lamotrigine for treatment of his seizures. He has experienced several partial seizures and one generalized tonic-clonic seizure. In addition, EEG shows epileptiform spikes from the left frontotemporal region. **Which one of the following is the best approach to monitoring lamotrigine efficacy in this patient?**

- A. Keep lamotrigine serum concentrations in the therapeutic range.
- B. Monitor serial EEG recordings for elimination of epileptiform activity.
- C. Monitor Quality of Life in Epilepsy scores.
- D. Monitor seizure counts with a seizure calendar.

18. A 67-year-old woman with atrial fibrillation has a left hemispheric stroke involving the cortex and resulting in aphasia and a paralyzed right side.

Which one of the following is the best approach to the use of AEDs in this patient?

- A. Initiate phenytoin when she presents to the emergency department.
- B. Initiate gabapentin 7 days after her stroke.
- C. Initiate lamotrigine if she experiences a seizure.
- D. Initiate carbamazepine when she is discharged from the hospital.

19. A 68-year-old woman has taken phenytoin for her seizures for 35 years. Her seizures are well controlled on 400 mg/day, and she has few adverse effects. She is also receiving lisinopril for hypertension and risedronate for osteopenia. She comes to the pharmacy today, asking for a nonprescription product for heartburn and indigestion. **Which one of the following products is best for this patient?**

- A. Cimetidine.
- B. Omeprazole.
- C. Calcium carbonate antacid.
- D. Famotidine.

20. A 79-year-old man has been taking regular-release carbamazepine 200 mg twice daily for 6 months for epilepsy. His seizures are well controlled, but he experiences dizziness and diplopia 3–4 hours after taking his dose. **Which one of the following is best to resolve this patient's problem?**

- A. Change carbamazepine to 100 mg four times/day.
- B. Change carbamazepine to 400 mg sustained release once daily.
- C. Reduce carbamazepine to 150 mg twice daily.
- D. Change carbamazepine to gabapentin 600 mg twice daily.

