

Treatment of Epilepsy in 3 Specialized Populations

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Presentation Summary

When discussing the treatment of epilepsy, targeted populations need to be defined. Three patient groups, children, the elderly, and women, are considered "special" because of metabolic and physical differences that require particular care during treatment of this disease. Treatment options vary significantly among these populations. Metabolic differences in very young and elderly patients require close attention by the prescribing physician. Rates of metabolism in children may be much faster than in nonelderly adults, requiring dosing adjustments to ensure enough medication is used to control seizures. Additional concerns with treating children include their increased sensitivity to toxic effects. Elderly patients may have slower metabolic rates because of decreased renal or hepatic function, and thus these patients can easily be overdosed as toxic drug levels build when clearance is reduced. Many elderly patients also may have concomitant illnesses that require other chronic medications. The potential for drug interactions is very high among this population. Women are considered a special population because of issues related to contraception, childbirth, and breast-feeding. Some antiepileptic medications are known to reduce the efficacy of oral contraceptives, and no medication has been proven safe for pregnant women. The pharmacokinetic profiles of many new generation antiepileptic medications may be advantageous to these specialized populations by creating fewer adverse effects, cleaner metabolism, and the reduced risk for drug interactions and teratogenicity.

Epilepsy is a very individualized disease. People are affected differently, and treatments must be tailored to be effective. Three "special" populations can be defined: the elderly, women, and children. The majority of epilepsy patients fall into one of these categories.

Epilepsy can be defined as a disorder of the central nervous system that manifests as seizures.¹ It is important to make this distinction because there are a number of other conditions that can result in seizures. A person who has only one seizure but whose magnetic resonance imaging (MRI) scan shows a glioma has epilepsy. A patient with diabetes who has multiple seizures as a result of hypoglycemia, however, does not have epilepsy. The old criterion defining epilepsy as 2 or more seizures is outdated, but most epidemiological studies have used that as a definition. Nevertheless, these current studies reveal startling information about the incidence of epilepsy. Data from a recent review of the occurrence of epilepsy during a 50-year period indicated that the cumulative appearance through age 74 was 3.0%, making it the most commonly occurring serious neurological disorder affecting all age groups.¹ During the first year of life the incidence of epilepsy is high but decreases as children age. What may be unknown to many, however, is that the highest incidence occurs in people who are 75 years of age and older.² As the number of elderly people in the population increases, we can expect an

increase in the incidence of epilepsy (Figure 1).

Study Results in Special Populations

Few drug and pharmacokinetic studies have been conducted for these special populations. Pregnant women are excluded from trials, and there are very few studies of children and elderly patients with epilepsy. Researchers often claim that studies of antiepileptic drugs (AEDs) include elderly patients, but the proportion of patients in the total study sample who are 65 years of age and older is usually too small to draw statistical conclusions. Pharmacokinetic studies usually include healthy individuals who were studied for very short durations. The populations studied most often include nonelderly men, but data from these individuals cannot accurately be extrapolated to apply to women, children, or the elderly. This causes problems when study data are used to develop practice guidelines that are intended to be used for all epilepsy patients. If the guidelines do not include provisions for special populations, limitations should be clearly stated.

Treating Elderly Patients with Epilepsy

The percentage of elderly people in the United States will continue to climb over the next few decades. In 30 years, more than 20% of the population will be 65 years of age or older. The fastest growing segments are people 85 years of age and older and 100 years of age and older.³ Current epidemiology data show a 1.5% incidence of active epilepsy in people who are 75 years of age and older.² By calculating population trends, we can estimate that by the year 2010 at least one third of new-onset epilepsy will be in individuals who are older than 65 years of age.

An important consideration for this population is nursing home care. Research conducted by MINCEP Epilepsy Care through a grant from the National Institutes of Health reveals that approximately 10% of the estimated 1.5 million elderly people residing in nursing

homes receive AEDs.⁴ These people are also taking, on average, 6 other medications. About 60% receive phenytoin, with the remainder receiving carbamazepine, phenobarbital, or valproate. Figure 2 lists the other types of medications these patients take besides AEDs. An alarming trend can be seen in the number of patients who are receiving psychotropic medications in addition to AEDs. Because many old generation AEDs cause some degree of cognitive impairment, the combination with psychotropic medications is of particular concern. Patients with cognitive dysfunction caused by Alzheimer's disease or other age-related illnesses may be particularly sensitive to these effects. Additionally, the number of medications taken with AEDs complicates treatment and increases the risk for drug interactions.

A common problem faced by elderly patients with epilepsy includes an age-related decrease in metabolic rate, which often requires adjustments to medications. It is not uncommon for elderly patients to be overmedicated. Concomitant illness requiring medications that often interact with AEDs can also increase the risk for drug interactions affecting either the AED or the other medication. Physicians treating elderly patients should expect the onset of age-related comorbidity and anticipate making adjustments to treatment regimens. Elderly patients who are treated on an outpatient basis may have memory problems that lead to poor compliance. This particular group should be monitored carefully.

Pharmacokinetic changes in elderly patients include reduced hepatic blood flow and liver volume, decreased renal clearance, and decreased protein binding. Blood level monitoring of AEDs is advisable for those agents that are renally eliminated.

In addition to problems with treatment, it is often a challenge to obtain an accurate diagnosis of epilepsy because there are other illnesses that produce symptomatic seizures. Elderly people are at higher risk for seizures from syncope influenced by cardiogenic causes, such

as arrhythmias, hypotension, and hypovolemia. People who faint and experience micturition may appear as having experienced an epileptic seizure. Despite the increased incidence of epilepsy among the elderly, these people should be thoroughly evaluated for other causes when presenting at an emergency department after a seizure. Failure to evaluate other possible causes could be extremely detrimental, especially if the seizure was the result of a cardiovascular disorder.

AEDs Commonly Used for Elderly Patients

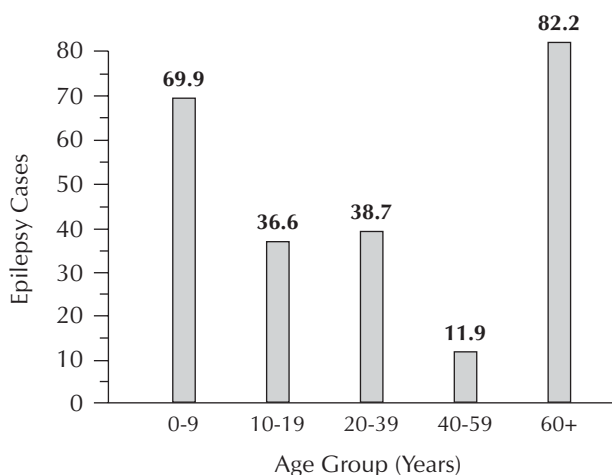
Phenytoin is the most commonly used AED in the elderly population. Problems with phenytoin include its high degree of protein binding (90%), which can obscure accurate blood levels,⁵ and its nonlinear pharmacokinetic profile, which can affect concentrations significantly. These changes in metabolism generally mean that doses lower than those traditionally used in younger adults should be prescribed. A dose of 3 to 4 mg/kg/day of phenytoin may be adequate, but most elderly patients are given much higher doses. Because phenytoin is

metabolized through the CYP 2C9 and CYP 2C19 hepatic isoenzyme systems, there is an increased risk of drug interactions with other medications metabolized along this same pathway.

Carbamazepine has similar metabolic problems. It is extensively metabolized through the CYP 3A4 and CYP 3A5 system, which is a very common metabolic pathway for many prescription and over-the-counter drugs. Concurrent administration of sildenafil or St. John's wort with carbamazepine, all of which affect the CYP system mentioned above, may result in decreased levels of carbamazepine and consequently increased seizures. Other agents, such as erythromycin and propoxyphene, which are well-known inhibitors of this metabolic pathway, can result in greatly increased levels of carbamazepine. The adverse effect of hyponatremia can occur in patients using diuretics in combination with carbamazepine. A general guideline is to provide only half the usual dose of carbamazepine to patients who are 80 years of age or older.

Valproate also has a high level of protein binding and other pharmacokinetic

Figure 1. Average Annual Incidence of Epilepsy by Age; New Cases per Year per 100,000



Source: Reprinted with permission from Leppik IE. *Contemporary Diagnosis and Management of the Patient with Epilepsy*. Newton, PA: Handbooks in Health Care; 2000.

characteristics that increase risks, such as platelet inhibition. Patients using valproate generally should not take aspirin because this combination may increase the risk of bleeding. Valproate has also been associated with tremors in patients with Parkinson's disease. There is some evidence in the medical literature that valproate may even trigger Parkinson's disease.⁶ More study is needed to draw an adequate correlation.

Better Options for Elderly Patients

The first step toward better treatment for elderly patients is to obtain an accurate diagnosis. Unlike younger patients, elderly patients probably need drug monitoring more often and regular testing to determine concomitant diseases. A thorough patient history can help identify risks for stroke and cardiac problems. Within the elderly population, there are differences in approaches to treatment. Selecting the appropriate method of treatment often depends on whether patients are healthy or have other medical problems.

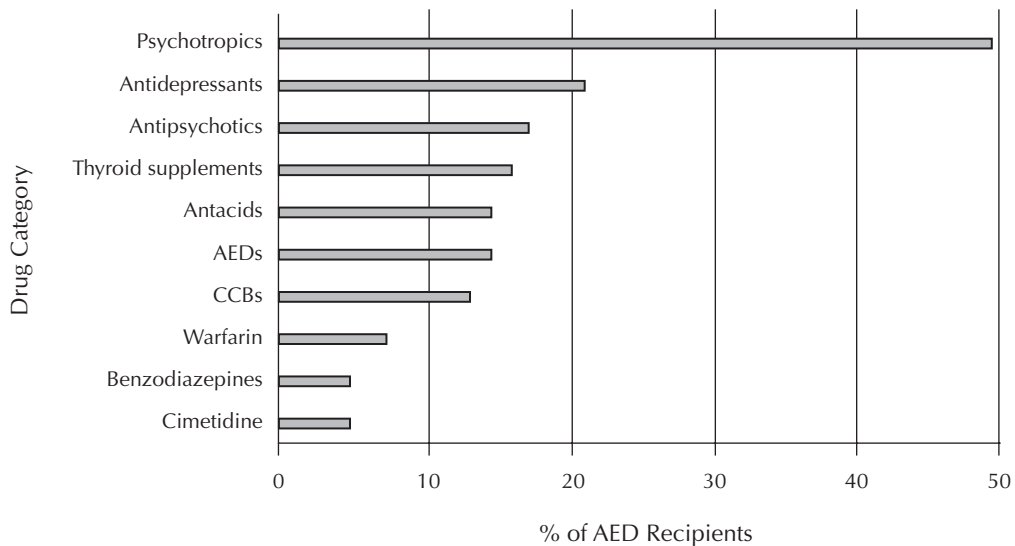
New generation AEDs, such as levetiracetam and gabapentin, may be more

suitable agents for elderly patients with epilepsy because these agents generally have low levels of protein binding and safer side-effect profiles than old AEDs (eg, phenytoin and carbamazepine). Because the new generation AEDs are excreted through the kidneys, this leads to less potential for drug interactions than agents eliminated through the liver. Elderly patients with other medical problems who are taking additional medications can benefit significantly by using a new AED. Management of elderly patients becomes much easier when risks for drug interactions are eliminated.

Treating Women with Epilepsy

There are an estimated 800,000 women of childbearing age with epilepsy in the United States. Issues of concern include the effect of AEDs on the efficacy of oral contraceptives as well as on fetal development. Important drug interactions between some AEDs and oral contraceptives have been noted. Specifically, phenytoin, phenobarbital, carbamazepine, topiramate, and oxcarbazepine have been shown to decrease the effectiveness of hormonal contracep-

Figure 2. Medications Commonly Used by Elderly Patients



AEDs = antiepileptic drugs; CCBs = calcium channel blockers.
 Source: Reference 4.

tives. Other AEDs, such as gabapentin, lamotrigine, levetiracetam, and tiagabine, do not affect the efficacy of oral contraceptives and may be better choices for women using this method of birth control.

The major issue facing women who plan to have children is teratogenicity. The Food and Drug Administration (FDA) has classified valproate and carbamazepine as known human teratogens (Schedule D). Samren and colleagues⁷ found that valproate produced a dose-dependent effect on fetuses that resulted in a significant increase (approximately 4%) in major congenital abnormalities.⁷ Carbamazepine was noted to produce about a 2% increase in major malformations. Polytherapy increased the risk for abnormalities, as would be expected. This study did not cover minor malformations. AEDs classified by the FDA as Schedule C include felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide. Drugs are classified as Schedule C when human teratogenicity is unknown. These drugs were not studied in pregnant women during clinical trials, but clinical use, since FDA approval, has not indicated teratogenicity. Prospective studies evaluating the teratogenic potential of newer AEDs are under way in the United States and Europe. Phenytoin has not been specifically classified as Schedule C or D because it was available prior to FDA classification for pregnancy risk. Another consideration is that AED drug levels change during pregnancy. Lamotrigine clearance rates may increase by more than 100% during pregnancy.⁸ Phenytoin clearance rates increase by 20% to 50%. These changes occur within the first 2 weeks of pregnancy, and drug levels remain low as a result of increased glucuronidation.

Women who are breast-feeding may also be concerned about the effects of using AEDs while nursing. There is no evidence that enough of the commonly used AEDs are present in breast milk to cause harm to children.

Treating Children with Epilepsy

The most important distinction to make for children who have had seizures is whether they are experiencing benign or malignant epilepsy syndromes. Benign causes include febrile convulsions (which are not considered to be epilepsy); childhood absence epilepsy; and benign Rolandic epilepsy. In contrast, Lennox-Gastaut syndrome and progressive myoclonic epilepsies are associated with mental retardation.

Table 1. Half-Life of Older Antiepileptic Drugs

Antiepileptic Drug	In Children t _{1/2} (hrs)	In Adults t _{1/2} (hrs)
Carbamazepine	6 to 15	10 to 25
Phenobarbital	40 to 70	50 to 120
Phenytoin	12 to 22	22 to 24
Valproate	4 to 8	10 to 12

t_{1/2} = half-life.

Source: Reference 1.

Table 2. Rate of Hepatic Fatalities by Age Group in Patients Receiving Valproate as Monotherapy or Polytherapy (1978-1984)

Age groups (yr)	Monotherapy		Polytherapy	
	Deaths	Rate per 10,000	Deaths	Rate per 10,000
0 to 2	1	1.42	15	19.01
3 to 5	1	0.92	3	2.41
6 to 10	3	1.22	4	1.45
11 to 20	0	0	5	0.86
21 to 40	0	0	4	0.60
41+	0	0	1	0.26
Total	5	0.27	32	1.52

Source: Reference 9.

Treating children differs from treating adults because cognitive effects of AEDs may be more serious than occasional seizures. Another concern is that half-lives of AEDs in children are different than they are for adults, as shown in **Table 1**. Because these medications are eliminated faster in children, doses generally have to be increased. This is especially true for drugs that are metabolized by the liver. New AEDs that are renally excreted may provide better options for children. Valproate should be used with care to treat children because it has been associated with hepatic fatalities (**Table 2**).⁹ Children younger than age 2 years are particularly at risk for hepatic failure, with much greater risk when valproate is used as part of a polytherapy regimen.

Conclusion

Although studies rarely include the elderly or children and always exclude pregnant women, the total number of patients with epilepsy who fall into these special populations is greater than those who do not. Age-related changes in metabolic function, concomitant use of medications, and concerns about pregnancy require special consideration for diagnosis and treatment. Elderly patients may benefit from new AEDs that provide cleaner pharmacokinetic profiles and less risk for drug interactions. Women using oral contraceptives should avoid AEDs known to reduce the effectiveness of these drugs, and valproate or carbamazepine should be used only when other AEDs are not effective, because these are known human teratogens. Faster metabolism in children requires

larger doses than those generally used in adults.

Many new generation AEDs provide improved options for treating special populations. Although more study focusing specifically on these patients is needed, current data suggest wider use of new AEDs may help epileptologists manage patients more easily and without concerns for the toxicity associated with the old generation agents.

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