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EPILEPSY (CW BAZIL, SECTION EDITOR)

Treatment of Epilepsy in the Elderly

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Abstract The treatment of epilepsy in older individuals is an increasingly important topic in neurology and an area that all treating neurologists should have familiarity with. As the population ages, the number of patients over 65 who present with new-onset epilepsy will increase, as will the complexity of their comorbid medical and neurological disorders. In older patients, seizures are often unwitnessed, or present with atypical symptoms, making the diagnosis more challenging. Additionally, there are relatively limited data to guide the use of anti-epileptic medications and other treatments in this patient population. Elderly patients may experience increased side effects from anti-epileptic drugs compared with younger patients and in general, are likely to have a narrower therapeutic window and greater degree of individual variation with respect to side effects. Familiarity with anti-epileptic medication dosing and titration schedules, possible adverse effects, and potential pharmacokinetic and drug interactions can be helpful when considering treatment options and may increase the likelihood of success.

Keywords Epilepsy · Seizures · Elderly · Anti-epileptic medication

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Introduction

Epilepsy is a condition that affects patients in all age groups. Estimates of prevalence vary, in part due to differing classifications and definitions of epilepsy and seizures, study methodologies, and the patient populations studied. A recent WHO publication on the public health aspects of neurological disorders estimated that approximately 50 million people worldwide have epilepsy, with about 85 % of those living in developing countries [1]. Epilepsy is more prevalent in patients over age 60, affecting close to 1 % of this group, and the prevalence appears to increase with age 0 [2, 3]. Most studies suggest that there is an increase in both incidence and prevalence of epilepsy in older patients [2, 4, 5]. An investigation of treated epilepsy in the UK General Practice Research database suggested that the incidence of treated epilepsy rises from 85.9 per 100,000 in patients aged 65–69 to 135.4 per 100,000 in patients over 85 years of age [2]. Several studies suggest that epilepsy is the third most common neurological diagnosis in elderly patients after dementia and stroke [2].

The treatment of elderly patients with epilepsy presents a unique series of challenges and opportunities. Most new-onset seizures in elderly patients are focal and often resulted from new underlying neurologic disease, such as cerebrovascular disease, neurodegenerative disorders, trauma, and neoplasm, though as with other age groups, a specific etiology cannot be identified in a large proportion of patients [5, 6]. The presentation of seizures can also differ in this population. Descriptions of the symptoms and semiologies may be variable or lacking, in part due to memory issues or lack of witnesses. Elderly patients are more likely to present with subtle or non-characteristic symptoms of seizures, such as syncope, memory problems, and confusional episodes or mental status changes, and classic auras and automatisms are less common [7, 8]. The relatively nonspecific nature of the symptoms often

leads to a delay in diagnosis. In the VA Cooperative Study 428, epilepsy was on the initial differential diagnosis in only a small proportion of elderly patients who were eventually diagnosed with epilepsy [7]. It is also important to note that a subset of elderly patients will experience acute seizures provoked by severe medical/metabolic abnormalities, abrupt medication changes, or direct medication effects (acute symptomatic seizures). These seizures do not always require long-term treatment. In those patients who are diagnosed with epilepsy and require ongoing treatment, consideration should be given to a number of factors. This article will review some of the general principles of treatment in elderly patients with epilepsy.

Medication Choice

When the diagnosis of epilepsy has been established, the primary treatment recommendation is typically an anti-epileptic drug (AED). While in some cases, the choice of AED is closely tied to a specific syndrome (for example, ethosuximide for childhood absence epilepsy), the majority of new-onset epilepsy in elderly patients is likely to be focal, and thus, many AED options may be appropriate, and medication selection focuses on those AEDs with efficacy in treating focal (and often secondarily generalized) seizures or those with a broad mechanism of action. In all patients with epilepsy, the choice of an appropriate medication involves an evaluation of several factors, including efficacy, potential adverse effects (both short and long term), interactions with other medications, feasibility/ease of use, and, increasingly, cost to the patient. There are limited head-to-head studies comparing efficacy of the AEDs and even less data specific to older patients. Evidence for best AED treatment for all adults has been extrapolated to the treatment of elderly patients, but only a few studies specific to this population have been performed. In a large randomized study of new-onset epilepsy among elderly patients in the Veteran's Administration, Rowan et al. compared the use of lamotrigine, carbamazepine, and gabapentin [9]. All three medications demonstrated similar effectiveness in treating seizures; however, lamotrigine and gabapentin were better tolerated than carbamazepine (possibly due in part to the use of standard release carbamazepine rather than sustained release). Several other studies have also suggested that lamotrigine is as effective as carbamazepine in this population and better tolerated than standard formulation carbamazepine [10, 11]. A recent updated review of the evidence for AED efficacy in the treatment of newly diagnosed epilepsy conducted by the International League Against Epilepsy (ILAE) noted that there have been a total of four randomized controlled trials examining monotherapy for partial onset seizures in elderly adults, only one of which produced class I data [12•]. On the basis of this data, it was concluded that lamotrigine and gabapentin were established (level A evidence) as effective initial monotherapy for treatment of partial onset seizures in elderly adults, whereas carbamazepine was possibly effective (level C), and topiramate and valproate (level D) were potentially effective. There are also studies that suggest that some of the newer generation AEDs such as oxcarbazepine, levetiracetam, and zonisamide may be safe and effective in elderly patients; however, few head-to-head or randomized trials exist [13–15]. Some limited randomized trials and subgroup analyses suggest that some of the newer AEDs, including levetiracetam, may be effective and have favorable pharmacokinetic profiles in elderly patients; considering these early in the course of treatment may be beneficial [16, 17]. More recently, a blinded clinical comparator trial compared retention rates in elderly patients with epilepsy randomized to carbamazepine (controlled release), lamotrigine, and levetiracetam. Seizure freedom rate (a secondary outcome measure) was similar among the three AEDs; however, patients randomized to levetiracetam had significantly higher retention rates (the primary outcome) compared with carbamazepine. Patients randomized to lamotrigine also demonstrated higher retention compared with carbamazepine, though this difference did not meet statistical significance [18•].

In general, anti-epileptic medications that are effective in the overall adult population are likely to be effective when used in elderly patients, and there are an increasing number of studies in the literature addressing efficacy in this age group. Newer generation AEDs appear in many cases to be comparable in terms of effectiveness, and may have several advantages over older generation medications, including more favorable side effect profiles, retention rates, and pharmacokinetic profiles, and often have fewer drug-drug interactions. Some of these considerations will be further discussed below.

Pharmacokinetic and Pharmacodynamic Considerations

The pharmacokinetic properties (absorption, distribution, metabolism, elimination) of AEDs are variable and often complex (Table 1). In elderly patients, there can be additional considerations which may necessitate adjustment of medication doses. Commonly, a decline in renal function and filtration/clearance is seen with age, resulting in decreased clearance and elimination. Many AEDs are metabolized by the hepatic cytochrome P-450 system. In some elderly patients, particularly those with other significant medical illnesses, hepatic function can decline, leading to decreased metabolism and the potential for elevated serum levels. Elderly patients commonly have lower lean body mass and increased body fat, which can affect both water and lipid soluble drugs. Older patients also commonly have lower serum protein and

Table 1 Commonly available anti-epileptic drugs and some features to consider when treating elderly patients. Not all drug effects are listed

Drug	Common side effects	Advantages	Potential disadvantages	Metabolism	Narrow or broad spectrum?
Phenytoin	Ataxia, nystagmus, gingival hyperplasia, decreased bone density	Widely available; can be rapidly loaded IV or PO	Non-linear kinetics; potent cytochrome P450 inducer; significant short-/long-term side effects	Hepatic	Broad
Phenobarbital	Somnolence, unsteadiness	Widely available, inexpensive, rapid loading IV or PO	Potent cytochrome P450 inducer; significant short-/long-term side effects	Hepatic	Broad
Primidone	Somnolence, unsteadiness	Inexpensive, can be used to treat tremors	Potent cytochrome P450 inducer; metabolized partially to phenobarbital	Hepatic	Broad
Carbamazepine	Nausea, hyponatremia, unsteadiness, nystagmus, double vision	Effective, easy to use, widely available, inexpensive	Potent cytochrome P450 inducer	Hepatic	Narrow
Valproic acid	Weight gain, hair loss, thrombocytopenia	Widely available, IV and PO formulation, broad spectrum	Cytochrome P450 inhibitor; potentially less effective for focal seizures	Hepatic	Broad
Vigabatrin	Fatigue, dizziness	Very effective in refractory epilepsy	Vision loss (non-reversible); cytochrome P450 inducer	Excreted renally with minimal hepatic metabolism	Narrow
Felbamate	Nausea, weight loss/anorexia	Broad spectrum use	Potential for bone marrow suppression	Partially metabolized hepatically	Broad
Topiramate	Cognitive dysfunction, fatigue, depression	Effective at treating generalized seizures; can be used to treat headaches	Can worsen cognitive function; increased risk of nephrolithiasis; weak cytochrome P450 inducer	Excreted largely intact; minimal hepatic metabolism	Broad
Zonisamide	Fatigue, cognitive dysfunction, depression	No significant effects on cytochrome system; broad spectrum	Increased risk of nephrolithiasis; sulfa moiety (cross reactivity)	Hepatic	Broad
Oxcarbazepine	Sedation, nausea, unsteadiness	Generally well tolerated; can be initiated relatively rapidly, effective for partial seizures; mood stabilization properties	Hyponatremia; mild cytochrome P450 inducer at higher doses	Hepatic	Narrow
Lamotrigine	Dizziness, nausea, fatigue	Generally well tolerated, may have some mood stabilization properties; effective for partial seizures	Must be started slowly due to increased risk of hypersensitivity reactions (Stevens-Johnson syndrome) with rapid uptitration; minimal hepatic induction at high doses	Hepatic via glucoronidation	Broad
Levetiracetam	Mood problems, fatigue	No significant medication interactions, IV and PO formulations, generally well tolerated; no effects on hepatic metabolism	Mood issues can be significant	Hydrolytic metabolism, renal excretion	Broad
Gabapentin	Fatigue, dizziness	Generally well tolerated, no significant medication interactions	Three times daily dosing, weight gain; peripheral edema	Excreted in urine unchanged	Narrow
Pregabalin	Dizziness, fatigue, cognitive slowing	Effective for many seizure types; can be used to treat neuropathic pain; no significant medication interactions	Peripheral edema, weight gain, angioedema	Excreted in urine unchanged	Narrow
Lacosamide	Unsteadiness, dizziness, diplopia	No significant medication interactions, IV and PO availability, no cytochrome induction	Possible cardiac conduction problems	Variable	Uncertain
Tiagabine		Minimal effects on cytochrome system		Hepatic	Narrow

Table 1 (continued)

Drug	Common side effects	Advantages	Potential disadvantages	Metabolism	Narrow or broad spectrum?
	Dizziness, fatigue, nausea, tremor		Narrow spectrum use; potential for induction of status epilepticus at high doses		
Rufinamide	Nausea, vomiting, dizziness	Effective in patients with suspected Lennox-Gastaut syndrome	Narrow spectrum use	Hydrolytic; renal excretion	Narrow
Ezogabine	Nausea, dizziness, ataxia	Unique mechanism of action (K+ channel opener)	Potential for visual/ophthalmologic changes; bluish discoloration of skin	Hepatic	Uncertain
Perampanel	Nausea, fatigue, weight gain	Unique mechanism of action (AMPA glutamate receptor antagonist)	Potential for serious mood issues	Hepatic via oxidation and glucoronidation	Uncertain
Clobazam	Fatigue, cognitive slowing	Generally well tolerated, appears effective in many seizure types	Somnolence	Hepatic	Uncertain/likely broad
Brivaracetam[a]	Fatigue, dizziness	No significant medication interactions ; possibly less mood-related side effects compared to levetiracetam	Irritability; minimal clinical experience	Hydrolytic metabolism; renal excretion	Uncertain

[a] FDA approved in early 2016; not yet widely available

albumin levels, which can result in an increased free fraction of protein bound drugs and potential toxicity [19, 20]. The pharmacodynamic profiles of AEDs can also be challenging in elderly patients. In particular, effects on balance and cognition are important to monitor. Elderly patients can be more sensitive to medication side effects at doses normally tolerated by younger individuals; therefore, it is often advisable to begin initial titrations at lower doses and to proceed more slowly with titration schedules (following the common adage "start low and go slow"). The idiosyncratic effects of individual AEDs are also important to consider. An example is the increased risk of hyponatremia associated with oxcarbazepine (and to a lesser extent carbamazepine) use. Hyponatremia is more common in the elderly population in general compared with younger adults, and thus, closer monitoring may be necessary.

Medication Interactions

AEDs with strong enzyme-inducing properties (such as phenytoin, carbamazepine, phenobarbital, and primidone) can increase the metabolism of other medications, including cardiovascular medications (anti-arrhythmics, anti-hypertensives), psychotropic medications and anti-depressants, cancer treatments, antibiotics/antimicrobials, other seizure medications, and anticoagulants (such as warfarin). This is not only the case with initiation of these AEDs but also with dose adjustment and withdrawal, necessitating close communication between the patient's neurologist and other treating physicians. In elderly patients who are often on multi-drug regimens, this can be challenging, particularly if other care providers are not familiar with these interactions. The newer generation of AEDs (including levetiracetam, lacosamide, and lamotrigine) are less likely to be associated with potent enzyme-inducing activity, or may do so only at higher doses. Inhibitors of hepatic metabolism (such as valproic acid) are somewhat less problematic but nevertheless require close monitoring.

Comorbid Conditions

Many elderly patients with epilepsy have underlying medical conditions which should be taken into consideration when treating seizures. As described previously, many AEDs have interactions with medications used to treat other disorders, often by their enzyme-inducing effects on the hepatic cytochrome system (phenytoin, carbamazepine, phenobarbital, mysoline). In patients who are required to take several drugs, several of the newer generation AEDs with no significant drug-drug interactions are attractive options (levetiracetam, lacosamide, gabapentin), as are those with enzyme-inducing

properties that typically occur only at higher doses (lamotrigine, oxcarbazepine).

A particular concern in the elderly is the issue of decreased bone density (osteoporosis), particularly in women. Many of the AEDs, especially those with strong enzyme-inducing properties, have been associated with decreased bone density (osteoporosis) with chronic use, likely from induction of vitamin D metabolism, which may lead to an increased risk of fractures [21, 22]. Interestingly, non-enzyme-inducing AEDs (such as valproate) have also been implicated in bone density loss [23, 24]. While there are no specific practice parameters or dosing guidelines regarding treatment, several prospective trials have been published suggesting that supplementation with calcium and vitamin D (and possibly risedronate) may result in improved bone mineral density in patients with epilepsy on AEDs; higher doses of vitamin D at 4000 IU/day may be more effective than low doses at 400 IU/day [25, 26]. In some cases, physicians and patients may elect to transition to newer generation AEDs, which generally have fewer negative effects on bone density; however, for various reasons this may not always be possible. For those patients on higher risk AEDs, many clinicians and professional societies suggest regular monitoring of vitamin D levels, along with supplementation of calcium and vitamin D, regular exercise, and healthy meal choices. Regular bone density screening (DEXA scans) may also be considered, particularly for patients on strong enzyme-inducing AEDs, though no clearly defined screening intervals have been established. Finally, evaluation by an endocrinologist can be helpful in patients who continue to have decreases in bone density despite these recommendations.

In the recent years, the association between mood disorders and epilepsy has been increasingly recognized. Mood and psychiatric issues are very common in patients with epilepsy, and there is some evidence to suggest that mood-related symptoms may even precede onset of epilepsy, suggesting a possible bidirectional relationship [27–29]. Recognizing the symptoms of mood disorders and treating them appropriately may have a variety of beneficial effects, including helping to improve mood, overall quality of life, medication adherence, and perception of medication side effects [30]. Treatment of mood may even improve seizure control and may affect surgical success [31]. There have been fewer studies focusing specifically on the role of mood in elderly patients with epilepsy; however, it has been reported widely that elderly patients in general are at higher risk for mood problems. Historically, a variety of screening instruments have been used to identify patients with depression. However, relatively few are validated for use in the epilepsy population. The most commonly used tools are the Beck Depression Inventory, which is a self-reporting instrument screening for depression, and the Neurological Disorder Depression Inventory for Epilepsy (NDDI-E), which screens for current episodes of depression [32, 33]. Recent research has validated use of the Hamilton Rating Scale for Depression, one of the most common screening tools for depression worldwide, in the epilepsy population [34].

Epilepsy Surgery

The literature regarding success rates of resective surgery in elderly patients is relatively limited. There are several published studies, though the number of participants tends to be small, and age ranges vary considerably [35–38]. Overall, published reports and subgroup analysis suggest that efficacy rates are relatively similar compared with younger adults, and that the factors which portend better outcomes are also comparable. Several of the studies suggest that while surgical outcomes may be comparable, the rates of neurologic complications such as cognitive deficits may be slightly higher in the elderly population.

Devices

There are two FDA approved devices for treatment of focal epilepsy in adults: vagal nerve stimulation (VNS) and responsive neurostimulation (RNS). There is a relative paucity of data regarding efficacy and tolerability in the elderly population; however, both may be considered as treatment options, and there is some data to suggest that the age of epilepsy onset or VNS implantation may not affect long-term efficacy of the device, and that the likelihood of VNS success in older patients is comparable to that in younger adults [39, 40].

Conclusions

Epilepsy is a common disorder in elderly patients, with increased incidence and prevalence in later life. The diagnosis itself can be challenging, as many elderly patients with epilepsy may present with symptoms that are somewhat nonspecific or subtle. The majority of new-onset epilepsy in older patients is focal in nature and results from a variety of etiologies. The primary treatment option for most patients is an anti-seizure medication. There are limited data available regarding comparative efficacy of these medications in older patients; however, most AEDs that are effective in younger adults are likely to show similar benefits in the elderly, and there are a few recently published studies in the literature which suggest that this is the case. In clinical practice, the comparative efficacy of anti-seizure medications in this population is sometimes less critical than the pharmacodynamic side effects and interactions that these medications can produce. Anti-seizure medications can be associated with a variety of short- and long-term side effects. Some of these can also exacerbate

underlying comorbid medical conditions, which are often present in greater prevalence in elderly patients. The pharmacokinetic profiles and drug-drug interactions of these medications can also be complex. These factors must all be considered in the selection of an appropriate anti-seizure medication. For all of these reasons, consideration of a newer-generation AED as initial monotherapy may be advantageous. Finally, although relatively less data exists in the elderly population for the use of non-medication treatments such as resective surgery and devices, these are also viable options and should not be excluded from consideration.

Compliance with Ethical Standards

Conflict of Interest Paul V. Motika declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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