Epilepsy in the elderly: Special considerations and challenges

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Abstract

The elderly are generally defined as those over 60 or 65 years old, but they are a heterogeneous group and may be subdivided into categories based on age and health status. The incidence of epilepsy is highest in the elderly. With a progressive increase in life expectancy, this is the fastest growing segment of patients with epilepsy. Older patients most often have focal seizures, with less prominent auras and automatisms, and longer duration of postictal confusion compared to younger patients. Status epilepticus is common and has a high mortality. The most common specific etiology is cerebrovascular disease, but the cause remains unknown in many patients. Diagnosis can be challenging because of several patient-related, physician-related and investigation-related factors. Over-diagnosis and under-diagnosis are common. Treatment is complicated by the presence of physiological changes related to aging, co-morbidities and cognitive problems as well as concerns regarding drug interactions and medication adherence. Seizures can be controlled in most patients with low doses of a single anti-epileptic drug (AED). Tolerability is an important factor in selection of an AED, as elderly patients tend to be highly sensitive to side effects. Drug-resistant epilepsy is uncommon. Epilepsy surgery, especially temporal lobectomy, can be performed in older patients with good results. More studies addressing the pathophysiological mechanisms of epilepsy in this age group, and greater inclusion of the elderly in clinical trials, as well as development of comprehensive care models are needed to provide optimal care to these patients.

Key Words

Diagnosis, elderly, epilepsy, treatment

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Introduction

There has been a progressive increase in life expectancy in the general population over the last several decades. This trend is likely to continue, and it has been suggested that the first person to live up to 150 years may have already been born! Epidemiological studies indicate that the incidence and prevalence of epilepsy is the highest in the elderly.[1] Thus, among patients with epilepsy, elderly persons constitute the fastest growing segment.

This group presents unique challenges in terms of diagnosis and treatment because of differences in the clinical presentation and etiology as compared to younger persons, presence of co-morbidities and cognitive difficulties in a significant proportion of patients, and physiological changes that affect pharmacological management. Despite the magnitude and complexity of the problem, surprisingly little clinical and basic research has been done in this population.

This article reviews our current understanding of the special issues that need to be considered in the diagnosis and treatment of epilepsy in the elderly. The emphasis is on epilepsy beginning in the elderly, rather than epilepsy starting at a younger age and persisting into later life.

Concept of "Elderly"

Most studies and reviews on the subject have considered the elderly to be 65 years or older, but some have included persons over the age of 60. The age of 65 has been generally accepted as a line of demarcation. However, from a medical standpoint, aging is a gradual process and there is considerable variation in the age at which a person manifests the physiological changes consistent with aging. Further, persons over the age of 65 are a heterogeneous group. With more people living into their nineties and beyond, the elderly have been divided into 3 groups based on age: "young-old" (65-74), "middle-old" (75-84) and "old-old" (> 85). Leppik [2,3] has proposed further subdivisions in each group based on health status: patients with only epilepsy, patients with epilepsy and multiple medical comorbidities, and the frail elderly, so that there would be a total of nine categories. Further, there is a difference

Access this article online

Quick Response Code:

Website:
www.annalsofian.org

DOI:
10.4103/0972-2327.128645

between elderly persons living independently and those living in nursing homes. Ideally, studies addressing epilepsy in the elderly should focus on specific subgroups because management strategies may differ within this population based on health status.

Epidemiology

Several studies in Europe and USA have consistently shown that the incidence of acute provoked and unprovoked seizures, epilepsy, and status epilepticus is higher in the elderly as compared to the younger population. In the USA, Hauser and Hesdorffer[4] noted an increase in the incidence of seizures beginning after age 50, and rising to 127/100,000 person-years in those aged 60 or older. In another study of a racially diverse, community dwelling elderly cohort, Hussain et al.,[5] found an incidence of 10.6/100,000 person-years in those between 45-59 years old, 25.8/ 100,000 person-years for the ages 60-74 and 101.1/100,000 person-years for the ages of 75-89. The prevalence rate of epilepsy in persons 65 years or older is approximately 1.5%. In a recent study,[6] the annual mean incidence of epilepsy in the elderly was 2.4/1000 persons and prevalence rate 10.8/1000 among US Medicare beneficiaries. Similar numbers have been observed in the UK, with an annual incidence rate of 85.9/100,000 in those between 65 and 69 years, and more than 135/100,000 for those older than 80.[7] In Finland, Sillampaa et al.,[8] found that the incidence of epilepsy increased from 1986 to 2002 in the elderly, but decreased in children and younger adults. In a small study of 23 elderly patients from South India, Thomas et al.,[9] noted that a first seizure was a frequent symptom among those attending Neurology clinics.

The prevalence of epilepsy is higher among nursing home residents than in community-dwelling elderly people. Based on use of antiepileptic drugs in 10%-11% of nursing home dwellers, with phenytoin being prescribed for approximately 60% of these patients, it has been estimated that the prevalence of epilepsy may be at least 6% in this population.[10]

The true incidence and prevalence of epilepsy in the elderly may actually be two to three higher than the numbers quoted above because of difficulties in identifying seizures and diagnosing epilepsy.[11]

Status epilepticus has also been reported to be more frequent in the elderly. In patients who are 60 and older, the annual incidence is 86/100,000, which is almost twice that seen in the general population. It is even higher after the age of 70 years. Mortality also increases progressively with age, etiology, and duration of status. In general, the mortality in the elderly is 38%, but increases to almost 50% in those greater than 80 years old.[12] Non-convulsive status epilepticus has a poorer prognosis in the elderly than in younger patients, because of underlying processes rather than the duration of status, and is associated with a high rate of hospital-acquired infections, which could be fatal.[13]

Types of seizures and epilepsy syndromes
Focal seizures are more common than generalized seizures in the elderly. The clinical manifestations of focal seizures are different from those noted in younger adults [Table 1]. An aura is less common and, if present, tends to be non-specific (such as dizziness). Automatisms are usually not present and seizures may manifest only with a blank stare and impairment of consciousness.[14] Postictal confusion tends to be prolonged in the elderly, lasting for hours and sometimes days to weeks, and may lead to an erroneous diagnosis of dementia. In one study,[15] secondarily generalized tonic-clonic seizures were found to occur in only 26% of elderly patients, as opposed to 65% of younger adults.

The clinical differences may be related to the anatomical origin of seizures, which is more likely to be mesial temporal in younger patients and extratemporal, especially frontal, in the elderly.[14] Extratemporal lobe localization is common as the most common etiology is stroke. New onset temporal lobe epilepsy can also occur. This can occur with or without hippocampal sclerosis.[16] In a retrospective study assessing the relationship between limbic encephalitis and late onset temporal lobe epilepsy,[17] four main etiologic subgroups were identified: idiopathic and secondary hippocampal sclerosis (due to generalized convulsive status epilepticus, head injury, old infarct), definite limbic encephalitis and MRI-defined possible limbic encephalitis. Limbic encephalitis was paraneoplastic or non-paraneoplastic.

Primary generalized seizures may also occur for the first time in the elderly, with a report of myoclonic seizures beginning at age 75, in one study.[18] Absence seizures and status epilepticus are infrequent, but at times there may be a history of childhood-onset absence that has resolved, only to recur in later life with or without generalized tonic-clonic seizures.[19] Limited studies performed in patients with late onset idiopathic generalized epilepsy suggest that, apart from the age of onset, the clinical features and response to treatment are not substantially different.

Etiology
The reported prevalence of specific causes depends on a number of factors including the definitions used, the populations studied and the investigative methods used.[20-23] However, some general observations can be made [Table 2]. The majority of patients have symptomatic epilepsy, and cerebrovascular disease appears to be the most common etiology of epilepsy in the elderly based on multiple studies in developed as well as developing countries.[9,14,23-25] Less frequent causes include neurodegenerative diseases such as Alzheimer's disease, trauma and brain tumors. Other causes are less common. In a substantial proportion of patients, the etiology is unknown. With advances in clinical evaluation and neuroimaging, this number is likely to decrease in the future.

Table 1: Differences in seizure symptomatology between the elderly and young adults[14,15]

Feature	Elderly	Young adults
Aura	Infrequent, non-specific	More common
Automatisms	Less common	Common
Secondary generalization	~26%	~65%
Postictal confusion	Hours to days	5-15 minutes

Table 2: Etiology of epilepsy in the elderly [3,14,23-25]

Cause	Frequency (%)
Stroke	20-50
Dementia	10-20
Brain tumor	10-30
Head injury	5-20
Other known cause	2-20
Unknown	20-50

Idiopathic generalized epilepsy beginning in the elderly is much less common. As in younger patients, acute symptomatic seizures can arise from drugs, metabolic derangements, infection, acute stroke, and head injury. Not all these patients will develop epilepsy.

Cerebrovascular disease
 20% to 50% of epilepsy in the elderly is related to cerebrovascular disease. Conversely, about 10% of patients with stroke are at risk of developing seizures within 5 years.[26] Seizures can occur with infarcts, intracerebral hemorrhage and subarachnoid hemorrhage. Hemorrhagic strokes are more likely to be associated with seizures than infarcts.[26-29] Transient ischemic attacks have a relatively low incidence of seizures.[30] Both early (< 2 weeks) and late (>2 weeks) seizures can occur and different mechanisms have been proposed for each type. About one-third of patients with early and one-half of patients with late post-stroke seizures develop epilepsy.[28,30] Predictors of seizures with ischemic stroke include severity (initial and persistent), large size, embolic cause, and involvement of the cortex, hippocampus or multiple brain areas.[31,32] Seizures may be less likely to occur with occlusions related to cervical dissection than with atherosclerotic occlusions.[33] The relationship between stroke and seizures may be bidirectional in the elderly, as some studies have shown that the risk of stroke is increased by nearly three-fold in patients with late-onset seizures.[34] It is therefore advisable to investigate patients with late-onset seizures for stroke risk factors and treat them appropriately.

There is limited understanding of the pathophysiological mechanisms underlying post-stroke seizures. Experimental animal models have used neonatal or young animals rather than aged ones. In human studies, the presence of multiple comorbidities such as hypertension, hyperlipidemia, and diabetes can alter the homeostatic mechanisms within the ischemic penumbra. Most of the experimental studies have addressed early seizures rather than late seizures.[35] Early seizures may be related to acute changes such as metabolic derangements (increased penumbral sodium and intracellular calcium), excessive glutamate, downregulation of gamma aminobutyric acid (GABA)ergic inhibition, hypoxia, hypoperfusion, and irritation by blood products. Late seizures likely result from chronic abnormalities such as scarring, changes in neuronal excitability, and hemosiderin deposition.[36]

Neurodegenerative diseases
Approximately 10%-20% of epilepsy in the elderly is due to dementia and neurodegenerative diseases associated with cognitive impairment. Alzheimer's disease is the best studied condition, and has been found to be associated with a higher rate of epilepsy than other dementias. Patients with Alzheimer's disease have a ten-fold higher risk of epilepsy and 10-22% of patients with Alzheimer's have seizures.[37] The incidence of seizures increases as the disease progresses, but seizures can occur even in early stages.[38] In patients with early-onset dementia, beginning at age 50-59, the risk of epilepsy has been estimated to be 87 times higher than that noted in the general population.[39] Both partial seizures and generalized seizures may occur.[25] Recognition of seizures can be difficult in patients with dementia but most patients respond well to anti-epileptic medications.[24]

The pathophysiological mechanisms of epilepsy associated with Alzheimer's disease are not clear. Experimental animal models provide limited data as spontaneously occurring neurofibrillary tangles or cerebral beta-amyloidosis have not been found in rodents or lower-order species, and, although there are transgenic mouse models that generate beta-amyloid plaques, they do not develop dementia resembling that seen in humans.[35] In human amyloid precursor protein (hAPP) mice, it has been observed that there is neural network dysfunction in excitatory and inhibitory systems resulting in spontaneous seizures, and epileptiform activity decreases with reductions in tau. Based on these findings, it has been suggested that interplay of beta-amyloid, tau, and the tyrosine kinase Fyn may result in network excitability in the hippocampus, and that reduction of tau may be helpful in preventing the development of spontaneous seizures.[35] A recent study[40] found that reduction of tau decreased seizure sensitivity in models of epilepsy not related to Alzheimer's disease, including the *Kcna1-/-* knockout mouse model of temporal lobe epilepsy and bang-sensitive *Drosophila* mutant models. They suggested that tau may play a general role in regulating intrinsic neuronal hyperexcitability independent of amyloid-beta overexpression and that reduction of tau may have broader therapeutic potential in epilepsy.

The incidence of epilepsy in fronto-temporal dementia is not well known. However, seizures can occur in the variant associated with rapidly progressive, severe dementia, and Parkinsonism that is linked to chromosome 17.[41]

Interestingly, the association of epilepsy with Parkinson's disease appears to be infrequent and, in a patient with temporal lobe epilepsy, a dramatic decrease in seizures was noted after onset of Parkinson's disease.[42] It has been suggested that D1 agonists may have a proconvulsive effect and D2 receptor stimulation could have an anti-convulsive effect.[43]

Trauma
Head trauma accounts for up to 20% of epilepsy in the elderly. Age of 65 years or more has been identified as one of the risk factors for developing epilepsy after a head injury.[24] Seizures may themselves lead to falls.

Brain tumors
Tumors are responsible for 10% to 30% of seizures in the elderly. They are more likely to occur with low grade slowly growing primary tumors.[24,44]

Diagnosis

As with younger patients, a detailed history should be obtained not only from the patient but also from an eyewitness, if available. This is particularly important in the elderly as they may have cognitive impairment and may not be able to provide an accurate history. Unfortunately, events may not have been witnessed as elderly people often live alone.

The diagnostic approach in the elderly remains the same as in younger patients. The first step is to determine if the events are epileptic seizures or non-epileptic in nature. Seizures may present in a variety of ways. Depending on the initial presentation, the differential diagnosis includes syncope, transient ischemic attacks, transient global amnesia, confusional migraine, drug intoxication, infections, metabolic disturbance, sleep disorders, psychiatric disorders, and dementia.

Transient or prolonged confusional states should prompt evaluation for complex partial seizures or non-convulsive status epilepticus, as elderly patients may not have prominent automatisms and postictal confusion can last for hours to days. The differential includes toxic, metabolic, and infective causes, and these may also provoke seizures. Blood tests such as a metabolic panel and lumbar puncture may be considered in acute situations. With recurrent falls, especially with loss of consciousness, syncope should be considered as an alternative diagnosis. Myoclonic jerks may occur with syncopal episodes and should not lead to an incorrect diagnosis of epilepsy. On the other hand, the mere presence of cardiac disease should not make the physician exclude epilepsy, as this is fairly common in the elderly. Syncope can be confirmed if typical symptoms occur in association with a recorded arrhythmia during prolonged electrocardiogram (ECG) recording or during tilt table testing.[24] In patients with transient memory loss, transient global amnesia should be considered if consciousness is preserved and it is an isolated event; complex partial seizures are associated with impairment of consciousness, and are more likely to recur. Visual auras may be epileptic or migrainous. As they may not be accompanied by headache in the elderly, it may be difficult to distinguish between migraines and occipital seizures.[45] If focal neurological symptoms occur, transient ischemic attacks (TIAs) should be excluded. In general, TIAs are more likely to be associated with negative symptoms (e.g. weakness, numbness), last longer and are rarely associated with impairment of consciousness, as compared to epileptic seizures.[24] If the events are characterized by movements during sleep, rapid eye movement (REM) sleep behavior disorder (RBD) is an important consideration in the elderly. With RBD, episodes tend to occur in the second half of the night, whereas seizures often occur during the first half, particularly nocturnal frontal lobe seizures.[24] Periodic limb movement disorder is another possibility. A video-polysomnogram is helpful in such patients. Psychogenic non-epileptic seizures can also occur in the elderly.

If the events are felt to be epileptic, provoking factors should be identified and treated. With unprovoked seizures, treatment further depends on whether the patient had a single seizure or recurrent seizures (epilepsy). Electroencephalography (EEG) and brain Magnetic resonance imaging (MRI) are the most important specific investigations.

A routine EEG, which usually identifies interictal abnormalities, may be of limited value in the elderly as it has low sensitivity and specificity. If a routine EEG is normal, an ambulatory prolonged EEG or video-EEG monitoring has been shown to be helpful in indentifying interictal epileptiform discharges and confirming the epileptic nature of recorded events. As part of the Veterans Administration Cooperative Study #428 (VACS #428),[14] 24- hour ambulatory EEGs showed interictal epileptiform discharges in 50% of patients, although no discharges were noted on routine EEG.[14] In a study using video-EEG monitoring in patients with an average age of 70 who presented with unclear attacks, McBride et al.,[46] were able to record typical events in 77 of 96 patients and confirm a diagnosis of epilepsy in 46 patients. Thirteen out of 27 patients with non-epileptic events had psychogenic seizures, and 26% of patients with non-epileptic events had interictal epileptiform discharges.

Brain MRI is the most helpful neuroimaging study, although cranial CT scans may be performed in acute or emergency settings. It is more likely to be abnormal in the elderly as compared to younger patients. A variety of structural abnormalities may be seen, most often those related to stroke. Findings in the VACS #428[14] included stroke in 43%, small vessel disease in 41%, diffuse brain atrophy in 35%, encephalomalacia in 9% and benign tumors in 1.5%. CT or MRI was normal in only 18%.

Due to a variety of factors [Table 3], epilepsy in the elderly may be overdiagnosed or underdiagnosed, or there may be a delay in diagnosis.[24,25] Some of the reasons for overdiagnosis include inappropriate use of anti-epileptic drug (AED) trials for non-specific symptoms without investigations, presumption that involuntary movements such as myoclonus, or incontinence during events represent seizures, misinterpretation of EEG findings and failure to include epileptologists in the diagnostic process.

Underdiagnosis is also common. In the VACS #428,[14] epilepsy was a diagnostic consideration during initial evaluation by primary care physicians in only 73% of patients who were ultimately diagnosed to have epilepsy. The most common initial diagnoses listed were blackout spells (29.3%), syncope (16.8%), altered mental status (41.8%) and confusion (37.5%). Generalized tonic-clonic seizures are more likely to be recognized than complex partial seizures, which are more common in this population.

Table 3: Reasons for mis-diagnosis of epilepsy in the elderly[24,25]

Patient-related:
   Often live alone, eyewitness may not be present
   May have cognitive impairment or other comorbidities
Physician-related:
   Patients are often seen by a primary care physician rather than a Neurologist
   Underdiagnosis due to different seizure symptomatology
   Overdiagnosis of falls, jerks or incontinence as epileptic seizures
Investigation-related:
   Low sensitivity and specificity of routine EEG

Treatment

Decision to treat

Patients with provoked seizures need to be treated for the underlying cause and usually do not need AEDs. With unprovoked seizures, the decision to treat depends on whether the patient had a single seizure or recurrent seizures (epilepsy). Unlike the situation in younger patients, anti-epileptic treatment may be appropriate after a single seizure in the elderly. This is because they have a high risk of recurrence, as they are usually partial and reflect focal pathology.[47] Patients with recurrent, unprovoked seizures clearly need to be treated. It is important to determine the etiology of the epilepsy, since seizures may be the first manifestation of a previously unrecognized condition, which may require specific treatment in addition to AEDs.

Pharmacological approaches

Initial treatment should be with a single drug (monotherapy). The choice of a specific AED depends on a number of factors including efficacy for the type of seizures and epilepsy, potential side effects (tolerability), physiological changes associated with aging, drug interactions, comorbidities, need for rapid titration and cost.

As most elderly patients have partial-onset seizures, almost all of the available AEDs (except ethosuximide) are effective.[47] Seizures are more likely to be easily controlled in the elderly as compared to younger patients. Mattson et al.,[48] noted that 62% of their patients over age 65 and only 30% of those aged 40 or younger, were seizure-free after two years. On the other hand, in the same study, it was noted that 64% of patients over age 65 had to stop taking an AED, compared to 33% of younger adults. Therefore, tolerability is a major factor in choosing an AED.

Several physiological changes occur with aging.[25,35,49] The ones relevant to pharmacotherapy are summarized in Table 4. Pharmacokinetic changes occur at all levels-absorption, distribution, metabolism, and elimination. Gastric secretion, blood flow, and gastrointestinal motility are lower and these may affect absorption. Reduction in serum albumin levels leads to reduction in protein binding and increase in free fraction of the drug. This is particularly significant for highly protein bound drugs such as phenytoin, carbamazepine, and valproic acid. While the increase in free levels may be beneficial in terms of producing therapeutic effects at lower doses, it also increases the risk of toxicity. Further, total serum concentrations may not be as useful a measure for monitoring drug levels, as the free fraction may be greater than that predicted by total serum concentrations. The elderly typically have a narrower therapeutic window (the range between the lowest effective concentration) and maximal tolerated concentration. Side effects are also more common because of earlier and steeper drug concentrations, which are related not only to higher unbound fractions but also to changes in half-life (e.g. phenytoin) and prolonged latency to steady-state levels. Drug concentrations may vary over time. In a study of nursing home residents, it was found that total phenytoin serum concentration varied by as much as three-fold on serial measurements despite no change in the dosage or use of other medications that could interact with phenytoin.[50] Increased proportion of fat in the elderly changes the distribution volume, so that it is increased for lipophilic drugs, such as phenobarbital and benzodiazepines, and decreased for hydrophilic drugs. Many AEDs are metabolized by the liver, particularly by the cytochrome P450 enzyme complex. The functional capacity of this system progressively decreases after age 40, and by the age of 70, it is about 30% lower. Similarly, renal clearance also decreases by about 10% every year after the age of 40. Pharmacodynamic changes include decreased receptor number and sensitivity, and the body's ability to maintain a stable serum drug level. Considering these factors and to minimize the risk of side effects, the old dictum of "start low, go slow" could be modified to "start lower, go slower" in the elderly.

The potential for drug interactions is extremely important in choosing an AED in the elderly as many of them take other medications for comorbidities. In the VACS #428,[14] approximately 25% of patients reported taking 15 or more prescription medications. Older AEDs such as phenytoin, phenobarbital, carbamazepine, and valproic acid are enzyme-inducers, and valproic acid is an enzyme inhibitor. These properties increase the likelihood of interactions with other medications. Newer AEDs with few or no interactions, such as lamotrigine and levetiracetam, may be more suitable for elderly patients who are on multiple medications.

The elderly may also have a variety of comorbidities that can complicate the diagnosis and treatment of epilepsy. Cognitive impairment is common and, in such patients, AEDs with cognitive side effects (e.g. topiramate and zonisamide) would not be optimal choices. Cognitive issues can also make it difficult for patients to adhere to treatment, provide accurate reports about seizure frequency and understand educational information.[24] Valproic acid may be associated with a higher risk of cognitive problems and Parkinsonism in the elderly.[25] The diagnosis of neurotoxicity from AEDs may be difficult in the presence of coexistent cerebrovascular disease and dementia. Phenytoin and carbamazepine may affect atrioventricular conduction and should be used with caution in patients with cardiac arrhythmias.[25] Osteoporosis is a major issue in the elderly and enzyme-inducing AED, as well as valproic acid have been shown to increase the rate of bone loss, leading to increased risk of fractures and other bone injuries. There is less evidence linking newer AEDs to impaired bone health. One study found that levetiracetam may decrease bone strength and bone formation, but not bone mass in rats.[51]

Table 4: Physiological changes during aging affecting pharmacokinetics and pharmacodynamics of AEDs[25,35,49]

Parameter	Decreased	Increased
Gastrointestinal motility, secretion,	+/−	
Serum albumin	+	
Body fat/lean mass ratio		+
Total body water	+	
Liver mass and blood flow	+	
Cytochrome P450 enzyme activity	+	
Renal blood flow and weight	+	
Glomerular filtration rate	+	
Filtration fraction		+
Receptor number	+	
Receptor sensitivity	+	

Conflicting results have been reported with regard to the effects of topiramate. Lamotrigine, at least as monotherapy, may not affect bone density.[52] Hip bone loss may be increased in men taking a non-enzyme inducing AEDs, such as gabapentin, according to one study.[53]

Rapid titration is necessary when patients have frequent seizures or status epilepticus. Choices often include AEDs that are available in parenteral formulations and can be given in loading doses, such as benzodiazepines, phenytoin/fosphenytoin, phenobarbital and valproic acid. Levetiracetam and lacosamide could also be considered. Anesthetic agents such as midazolam, propofol, and pentobarbital can be used in refractory status epilepticus. Among oral medications, topiramate given nasogastrically in doses ranging from 300 mg to 1600 mg has been shown to be effective in treating refractory status epilepticus.[54]

Cost and availability of medication are also major factors in choosing an AED, particularly in developing countries. Despite numerous concerns with older AEDs, they are more readily available and less expensive than newer drugs.

Evidence from clinical trials in the elderly
Few studies have specifically studied the efficacy and tolerability of AEDs in the elderly, so that the general approach has been to extrapolate the results of trials in younger adults while considering the physiological changes associated with aging. In fact, regulatory trials typically do not include this age group, although the pharmacokinetics of individual drugs are often studied separately.[55]

Only three randomized, controlled, double-blind trials have been performed in the elderly. [11,56,57] Two of these compared lamotrigine and carbamazepine. In the first study,[56] where the standard formulation of carbamazepine was used, both were found to be equally effective, but lamotrigine was better tolerated. In the second study,[57] the extended-release formulation of carbamazepine was used. This resulted in lower median carbamazepine serum concentrations (5.1 mg/l versus 6.7 with the standard formulation) and almost equal tolerability when compared with lamotrigine. The third study[11] compared 1-year retention rates, a measure of effectiveness combining efficacy and tolerability, for lamotrigine, gabapentin, and carbamazepine. Carbamazepine had a lower retention rate than the other two drugs, with a discontinuation rate due to adverse effects of 31% (12% with lamotrigine, 22% with gabapentin). Efficacy was similar with all three drugs, so that the difference in retention rate was largely related to lower tolerability of carbamazepine. The differences may be related to the use of a standard formulation rather than the extended release preparation of carbamazepine, and higher relative maintenance doses of carbamazepine.[24]

A randomized trial comparing low (50 mg) and high (200 mg) doses of topiramate found that both were equally effective as monotherapy, but two-thirds exhibited adverse reactions, including cognitive dysfunction. The overall incidence of adverse effects was similar for both dosages and only 18% (seven patients in each group) required discontinuation.[58]

Levetiracetam has been studied as adjunctive therapy in the KEEPER study where it was found that the seizure response rate among those 60 years and older was 81% versus 67% for those less than 60 years in the final 6 weeks of the study.[59]

Oxcarbazepine monotherapy at low to moderate doses resulted in seizure freedom for at least 1 year in 37.6% of elderly patients in a prospective study.[60] However, oxcarbazepine needs to be used with caution in the elderly as the incidence of hyponatremia increases with age and severe hyponatremia is more common with oxcarbazepine than carbamazepine.[25]

Response to treatment with AEDs
Elderly patients are more likely to respond to AEDs and at lower doses than required in younger patients. [24],[25],[35] Drug-resistant epilepsy is uncommon and its exact incidence in this population is unclear. Adherence to medications can be problematic due to cognitive and psychiatric comorbidities, as well as the cost of medications. In the VACS #428,[14] it was noted that approximately half of the patients had poor adherence. Adherence was lower for drugs with cognitive side effects such as phenobarbital, valproic acid and gabapentin, and higher for lamotrigine and levetiracetam. Most elderly patients receive long-term, often lifelong, treatment as it is unclear if AEDs can be safely withdrawn.[24,35,47]

Epilepsy surgery
For a variety of reasons, epilepsy surgery is less often performed in the elderly. Seizures are often and easily controlled with AEDs. Temporal lobe epilepsy is less common compared to younger patients. Presence of cardiovascular and other co-morbidities increase the risk of complications from surgery and social factors such as employment are less relevant.[25] Nevertheless, surgery has been successfully performed in this population. Most often this is done in patients with epilepsy beginning in earlier life, although surgery has also been performed in patients with new-onset epilepsy in later life. The oldest patient reported so far was 76 years old at the time of surgery.[61]

There are few published data and studies have used different criteria for identifying older patients. In addition, there was no comparison with a younger population in some studies and the duration of follow-up after surgery was variable. McLachlan *et al.*,[62] compared seizure outcome 5 years after temporal lobectomy in 20 patients older than 45 years with that in 68 patients who were younger. The oldest patient was 60-years-old. 30% of the patients who were >45 and 40% of the younger patients became seizure-free, but the differences did not achieve statistical significance. Complications were no greater in the older group than in the younger patients. Sirven *et al.*,[63] compared patients >50 years with those younger than 50, with the oldest patient being 66 years. 52% of older and 75% of younger patients became seizure-free after temporal lobectomy on follow-up at a mean of 4 years, which swas a statistically significant difference. However, post-operative neuropsychological outcome and driving status were similar in the two groups. Boling *et al.*,[64] found that 61% of 18 patients older than 50 (oldest was 64 years) became seizure-free after temporal lobectomy when followed-up for up to 64 months. Outcome was compared with those of younger patients with

temporal lobe epilepsy who were stratified by age. There was a trend to more seizure freedom and increased likelihood of returning to work or usual activities in younger patients, but the complication rate was comparable among the age groups studied. Grivas *et al.*,[65] studied 52 patients aged 50-71 years and obtained a seizure-free rate of 71%. There was no difference in seizure outcome between patients older than 50 and those over 60, and the results were not different from those in a younger patient group. Complications occurred in 7.7% and consisted of deep venous thrombosis, intracerebral hemorrhage, pneumonia and a small ischemic stroke. 3.8% had permanent neurological deficits (aphasia, hemiparesis) and 5.9% had hemianopia. In a small retrospective study of seven patients between 60 and 76 years old, Acosta *et al.*,[61] found that four became seizure-free. Complications were not reported. Tellez-Zenteno *et al.*,[66] described a 75-year-old patient who underwent temporal lobectomy for recurrent status epilepticus following resection of a suprasellar meningioma. He had only 2 complex partial seizures during 14 months of follow-up with no recurrence of status epilepticus. He had mild expressive aphasia lasting for a few days after surgery. Srikijvilaikul *et al.*,[67] compared seizure outcomes after anterior temporal lobectomy in 16 patients >50 years (range 50-72) with those in 184 younger patients (range 16-v49). All had unilateral hippocampal sclerosis. 56% of older patients and 79% of younger patients were seizure-free and post-surgical complications were more common in older patients (25% versus 4.4%).

From these studies, it appears that epilepsy surgery, especially temporal lobectomy, can be performed in older patients with good results. In general, seizure outcomes tend to be a little worse, and the rate of post-operative complications a little higher than in younger patients.

Conclusions

Epilepsy in the elderly is an important and growing problem. The clinical manifestations and causes are different from those in younger patients. The diagnosis of epilepsy can be challenging because of atypical presentation, different entities that need to be considered in the differential diagnosis, psychosocial factors, comorbidities including cognitive dysfunction, and non-specific abnormalities on routine investigations. Treatment can also be more difficult due to unique pharmacokinetic and pharmacodynamic changes, increased sensitivity to side effects, presence of comorbidities and drug interactions.

Several questions remain unanswered because limited basic research and clinical trials have been performed in this group. Does the aging brain become more prone to epilepsy? If so, can anything be done to reduce the change in seizure threshold? What is the role of the aging hippocampus? Why does status epilepticus occur more commonly in the elderly? What are the basic mechanisms of epilepsy related to stroke and neurodegenerative diseases? What are the problems of performing clinical trials in the elderly? What are the chronic complications of AED on bone health and other systems? There are also likely to be several "unknown unknowns."[3]

The natural history and prognosis of epilepsy in the elderly also need to be better understood. In the recently published study on epilepsy in US Medicare beneficiaries,[6] an unexpected finding was that, even though the incidence rates of epilepsy were higher in the elderly and continued to increase with age, the prevalence rates were not much higher than in the general population, and did not vary greatly with increasing age. The reasons for incident cases falling off prevalence counts are not clear, but possibilities include increased mortality from epilepsy, resolution of epilepsy, over estimation of incident cases or subsequent correction of an initial misdiagnosis of epilepsy.[68]

More studies specifically addressing these issues need to be performed in the future. The pathophysiological mechanisms underlying epilepsy related to stroke and neurodegenerative diseases need to be better understood. Identification of genetic and other biomarkers would be helpful in developing novel preventive approaches. A greater effort should be made to include elderly patients in clinical trials and to better understand the chronic adverse effects of AEDs in this population. The role of epilepsy surgery needs to be more clearly defined. Psychosocial factors as well as adherence to medications should be addressed. A more comprehensive care model for inpatient and outpatient care including primary care physicians, neurologists, epileptologists and nursing staff would be helpful in providing optimal care to these patients.[24]

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