

# Epilepsy in the Elderly: Treatment and Consideration of Comorbid Diseases

## Review

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Epilepsy is the third most common neurological disorder affecting older adults after stroke and dementia, and the incidence of epilepsy is increasing rapidly in this population. A further increase in the incidence and prevalence of epilepsy is expected in aging societies. The establishment of a correct differential diagnosis between epilepsy and other seizure disorders that are common in the elderly is crucial. The symptoms of seizures in the elderly may be different from those in younger populations. The diagnosis is difficult, probably because of nonspecific characteristics, short-term symptoms, and absence of witnesses. There are three important issues in the treatment of epilepsy in the elderly: changes in pharmacokinetic parameters, polytherapy (including non-antiepileptic and antiepileptic drugs), and susceptibility to adverse drug effects. Antiepileptic drugs (AEDs) with fewer adverse effects, including cognitive effects, and AEDs without significant pharmacokinetic drug interactions are needed. Several studies found that stroke was strongly associated with a high incidence of early seizures and epilepsy. Stroke is also one of the major causes of status epilepticus. Cortical involvement and large lesions are strongly associated with the development of seizures and epilepsy. The severity of the initial neurological deficit is a strong clinical predictor of seizures after ischemic stroke. The optimal quality of life of dementia patients cannot be achieved without a proper diagnosis of coexisting epilepsy. (2019;9:27-35)

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## Introduction

Epilepsy is the third most common neurological disorder affecting older adults after stroke and dementia. The incidence of epilepsy is increasing rapidly in the elderly, partly because of the increasing prevalence of stroke, dementia, and brain tumors. Considering that modern society is aging, the overall incidence and prevalence of epilepsy is expected to increase, and many patients with newly diagnosed epilepsy are older adults.

In addition to the increasing incidence of epilepsy in the elderly, special attention must be paid to take proper care of these patients due to associated age-related physiological changes, such as decreased renal and hepatic function, and the fact that many of these patients already have concomitant diseases and take many other drugs to control these problems. Furthermore, the characteristic symptoms of new-onset seizures in the elderly may be different from those in younger patients.

These factors should be considered collectively to achieve effective

and safe control of epilepsy in older adults.

## Incidence and prevalence of epilepsy in the elderly

The results of a recent United States national survey indicated that the incidence of epilepsy increased by 24% from 2010 to 2015.<sup>1</sup> Furthermore, the incidence of epilepsy and seizures has increased dramatically in individuals older than 60 years.<sup>2</sup> According to Medicare data, the estimated incidence and prevalence rates of epilepsy among older adults in the United States are 2.41/1,000 and 10.8/1,000, respectively.<sup>3</sup> The increase in the incidence of epilepsy with increasing age was confirmed by a community-based study, wherein the age-specific incidence was 10.6 per 100,000 person-years in the age group 45-59 years, 25.8 in the age group 60-74 years, and 101.1 in the age group 75 to 89 years.<sup>4</sup> The incidence of acute symptomatic seizures is also higher with increasing age. Seizures occur in approximately 10% of patients with stroke.<sup>5</sup> The re-

sults of the Cardiovascular Health Study showed that the prevalence of epilepsy increased from 3.7% to 5.4% during a 14-year follow-up<sup>6</sup> and confirmed that individuals with a history of stroke had a relatively higher risk of developing epilepsy.

The elderly are more prone to developing a first unprovoked seizure. The incidence of this complication was 52-59 per 100,000 in individuals aged 40-59-years and increased to 127 per 100,000 in people aged 60 years or older.<sup>7</sup> The recurrence rate after the first seizure was also higher in the older population:<sup>8</sup> 79% in the first year after the first seizure and 83% in the 3 years after the first seizure.<sup>9</sup>

Status epilepticus (SE) is two to five times more common in the elderly than in young adults, with an annual incidence of 86 per 100,000 in individuals older than 60 years.<sup>10</sup>

**Table 1.** Etiology of epilepsy and seizures in the elderly

	Value (%)
Epilepsy	
Cryptogenic epilepsy	~50
Stroke	30-50*
Dementia	10-20
Tumors	4-6
Trauma	1-3
Acute symptomatic seizure	
Acute stroke	30-54
Metabolic or electrolyte imbalance	10-15
Tumors	~10
Trauma	~10
Drug-related seizure	~10
Central nervous system infection	2-3

\*Epilepsy cases with known causes.

In the general population, after a first unprovoked seizure, the long-term risk of recurrence ranges from 25% to 52%.<sup>9,11,12</sup> Multivariate analysis showed that age, whether analyzed as a categorical or continuous variable, was not predictive of seizure recurrence. In the elderly subgroup, remote symptomatic etiology independently predicted recurrence,<sup>13</sup> and most of the individuals in this subgroup had symptomatic etiologies. A prospective study indicated that remote symptomatic etiology, first seizure arising during sleep, epileptiform abnormalities on electroencephalography (EEG), and partial seizures were positive predictors of the recurrence of epilepsy.<sup>13</sup>

The most common cause of epilepsy in the elderly is cryptogenic or stroke-related seizure, followed by dementia and tumors (Table 1).<sup>14-27</sup> Acute stroke is also a leading cause of acute symptomatic seizures. Other common causes of acute symptomatic seizures are toxic-metabolic events and trauma.

Given that small focal lesions with a vascular origin may not be detected by current neuroimaging techniques, vascular lesions, including small strokes, may be a much more common cause of epilepsy.

Some drugs can lower the threshold of seizures. However, the use of several medications by elderly individuals to treat other conditions may contribute to the occurrence of seizures (Table 2).

### Clinical presentation of seizures in the elderly and differential diagnosis

In the elderly, the most frequent type of seizure is complex partial seizure (CPS) without secondary generalization (47.1%), and temporal lobe epilepsy is the most commonly diagnosed epileptic disorder (71.4%).<sup>28</sup>

**Table 2.** Drugs and risk of seizures

Moderate risk	Intermediate risk	Low risk
Chlorpromazine Clozapine Olanzapine	Other antipsychotic agents	Quetiapine Risperidone
Clomipramine Maprotiline	Cyclic antidepressants Bupropion Methylphenidate	SSRIs MAO inhibitors
Pethidine	Tramadol Beta-lactam antibiotics Isoniazid Metronidazole Theophylline Aminophylline	Local anesthetics Antivirals Other antibiotics Quinolones Beta-blockers

SSRI, selective serotonin reuptake inhibitor; MAO, monoamine oxidase.

Typical auras, including fear, epigastric rising sensation, and déjà-vu phenomena, occur at a lower rate than usually nonspecific auras such as dizziness.<sup>29</sup> Postictal confusion may be longer than usual and typical symptoms, including orofacial and hand automatisms, are less common. Focal motor seizures and secondarily generalized tonic-clonic seizures are also less common.<sup>30</sup> The diagnosis of this condition is difficult, probably because of nonspecific characteristics, short-term symptoms, and the absence of witnesses among family members or surrounding people; moreover, the presence of retrograde amnesia caused by falls can further limit the correct diagnosis. Generalized tonic-clonic seizures usually cause falls when the patient is standing. However, other seizure types may also cause falls in the elderly.<sup>31</sup> Patient's complaints may vary with mental status, degree of confusion, and memory disturbance.<sup>29</sup>

Careful history-taking and analysis of the circumstances of events that preceded the symptoms, evaluation of patient posture, presence of myoclonic jerks and confusion, duration of events, and the recurrence of episodes may lead to a correct diagnosis. The recent widespread use of smartphones may allow family members to capture videos of seizures. Therapy using AEDs may be necessary in some cases because of inconclusive diagnosis due to atypical symptoms and nonspecific imaging on the EEG.

The differential diagnosis between seizures and syncope is difficult in some cases. The incidence of syncope is high in the elderly. Brief myoclonic jerks or tonic posturing is common in cases of syncope. Some characteristics are helpful in the differential diagnosis between these conditions (Table 3). In the case of cardiogenic syncope, the du-

ration of loss of consciousness may be correlated with the duration or degree of arrhythmia. The classical prodrome that occurs in vasovagal syncope is usually absent in cardiogenic syncope. Temporal lobe seizure may cause ictal asystole on rare occasions, leading to cardiogenic syncope.<sup>32</sup> The presence of a pacemaker may reveal the typical symptoms of temporal lobe epilepsy, including orolimentary or hand automatisms.

**Table 4.** Differential diagnosis of epilepsy and other seizure disorders in the elderly

Neurological
TIA
TGA
Endocrine/metabolic
Hypoglycemia
Hyponatremia
Cardiovascular
Vasovagal syncope
Sleep disorders
REM behavior disorder
Parasomnia, including sleep eating disorder or sleepwalking
Other reflex syncope
Sick sinus syndrome
Other arrhythmia
Postural hypotension
Psychological
Nonepileptic psychogenic seizure

TIA, transient ischemic attack; TGA, transient global amnesia; REM, rapid eye movement.

**Table 3.** Differential diagnosis of seizure and syncope

	Syncope	Seizure
Trigger (position, emotion)	Common	Rare
Sweating/nausea	Common	Rare
Pallor	Common	Rare
Unilateral symptom	Rare	Common
Cyanosis	Rare	Common
Duration of LOC	< 20 seconds	Minutes to hours
Movements	A few clonic	Tonic-clonic
Tongue biting	Rare	Common
Frothing	Rare	Common
Confusion	Rare, < 30 seconds	Common, >minutes
Myalgia	Rare	Common
Eyeball deviation	Upward	Lateral
Periorbital petechial hemorrhage	No	Yes

LOC, loss of consciousness.

Parasomnia is common in the elderly. In addition, many systemic and metabolic diseases cause acute confusion. Therefore, the differential diagnosis of epilepsy in the elderly is broad (Table 4).

### Critical issues in the treatment of epilepsy in the elderly

There are three relevant issues in the treatment of epilepsy for the elderly: changes in pharmacokinetic parameters, polytherapy (including non-AEDs), and susceptibility to adverse drug effects. Drug absorption may be significantly delayed or decreased because of a diminished ability to absorb AEDs in the intestinal tract. Hepatic and renal clearance is also reduced with aging. Furthermore, the glomerular filtration rate (GFR) declines by >50% between the third and eighth decades of life.<sup>33</sup> The decreased therapeutic window in the elderly may increase the vulnerability to the adverse effects of AEDs. The lower levels of serum albumin and higher levels of free AEDs may also contribute to dose-dependent adverse effects.

There are many concomitant diseases in the elderly, including cardiovascular problems, mild cognitive impairment, dementia, and diabetes mellitus. For this reason, these individuals are likely to take many medications concomitantly. Even healthy elderly subjects may take many drugs. In this respect, the AEDs that lack pharmacokinetic interactions present an advantage.

The elderly are prone to experiencing adverse events after taking AEDs. In addition to decreased hepatic and renal function, older in-

dividuals, especially older women, present changes in pharmacokinetic and pharmacodynamic (PD) parameters, and these changes may cause symptoms and impair the quality of life when drug dosage remains unchanged.<sup>34</sup> Receptor sensitivity may be heightened by PD factors, and homeostatic mechanisms may be impaired in the elderly. Other issues such as the effect of AEDs on bone metabolism, induction of atherosclerosis, and cognitive function are also important in this population.

Several comorbidities may cause epilepsy, including seizure-related trauma (especially in older adults with decreased bone mineral density) and psychiatric comorbidities (such as depressive mood, which may have a profound effect on the quality of life).

The general rule to avoid the occurrence of adverse effects caused by AEDs in this population is to "start low and go slow."<sup>35</sup> It is better to start AEDs at a dose lower than usual and increase the dose gradually in small increments.

### Suitable antiepileptic drugs for the elderly

Older patients with epilepsy usually respond well to AEDs.<sup>36,37</sup> The two most important factors to consider when selecting AEDs for these patients are pharmacokinetic drug interactions and adverse effects. The presence of adverse effects significantly impairs the quality of life of this population.<sup>38</sup> AEDs with a high therapeutic index are advantageous because of their pharmacokinetic characteristics. AEDs with fewer adverse effects, including cognitive effects, are

**Table 5.** Advantages and disadvantages of using AEDs in the elderly

AEDs	Advantages	Disadvantages
Carbamazepine	High efficacy	Relatively low therapeutic index, enzyme inducer, rash
Valproate	Broad spectrum, IV, rapid titration	Weight gain, encephalopathy, tremor
Gabapentin	Rapid titration, few AEs, no drug interaction	Limited efficacy, multiple-daily dosing, renal clearance
Pregabalin	No drug interaction	Somnolence, weight gain
Lamotrigine	Broad spectrum, no cognitive AEs, psychotropic effect	Rash, slow and complex titration
Levetiracetam	High efficacy, broad spectrum, rapid titration, IV, no interaction, no cognitive AEs	Psychiatric dysfunction, dose adjustment according to the GFR
Oxcarbazepine	High efficacy, better PK/AE profile than carbamazepine	Rash, hyponatremia
Topiramate	High efficacy, broad spectrum, low PK interaction	Cognitive AEs, weight loss, glaucoma, renal stone
Zonisamide	High efficacy, broad spectrum, low PK interaction, once-daily dosing	Cognitive AEs, weight loss, renal stone
Lacosamide	High efficacy, rapid titration, IV, no PK interaction, low cognitive SE	Dizziness, arrhythmia
Perampanel	Broad spectrum, long half-life	Somnolence, dizziness

AEDs, antiepileptic drugs; IV, intravenous administration; AEs, adverse effects; GFR, glomerular filtration rate; PK, pharmacokinetic; SE, status epilepticus.

needed because the elderly are more prone to experiencing these effects. AEDs without significant pharmacokinetic interactions are adequate to elderly patients who take multiple medications to treat other diseases. Moreover, AEDs without enzyme-inducing effects have advantages as they have fewer or no harmful effects on bone metabolism and the development of atherosclerosis.<sup>39</sup> Other specific characteristics of AEDs administered to these patients should be considered (Table 5).

Hepatic metabolism is reduced in the elderly, and the effects of AEDs that interfere with this metabolism (such as carbamazepine) can be minimized by slow titration. In addition, a reduction in the target dose may be necessary to avoid dose-dependent adverse events. The target dose of AEDs with renal metabolism (such as levetiracetam or pregabalin) may have to be reduced in cases in which creatinine clearance is reduced. The dose of high-protein-binding AEDs (such as phenytoin) should be reduced in cases in which albumin is decreased because the serum level of the free drug is high. Given that symptomatic hyponatremia occurs more frequently with the use of oxcarbazepine, especially in older individuals taking multiple medications, the serum levels of sodium should be checked regularly.<sup>40</sup> The combination of valproate and topiramate may lead to valproate-induced encephalopathy.<sup>41</sup> To improve compliance, long half-life and extended-release AEDs have the advantage of allowing once-a-day dosing.

The results of randomized controlled trials that compared carbamazepine with lamotrigine indicated that the efficacy of these drugs was similar; however, the tolerability of lamotrigine was better.<sup>42-44</sup> The results of a retrospective study that compared 10 AEDs administered to 10 or more elderly patients older than 55 years showed that lamotrigine had the highest 12-month retention rate (79%), which was significantly higher than that of carbamazepine, gabapentin, oxcarbazepine, phenytoin, and topiramate. The retention rate of levetiracetam (73%) was the second highest and was significantly

higher than that of carbamazepine and oxcarbazepine.<sup>45</sup>

## Stroke and epilepsy

Stroke is the most common severe neurological disorder. There is a strong association between stroke and epilepsy. The second Dutch National Survey of General Practice<sup>46</sup> involving 276,921 subjects showed that the prevalence of epilepsy was comparatively higher in people with stroke (odds ratio [OR], 8.4), and this result was corroborated by the Canadian Health Survey (OR, 10.62).

There are various definitions of epilepsy and seizures associated with stroke.<sup>47-52</sup> Early seizure is defined as seizures that occur within 7 or 14 days of any stroke, depending on the study. This type of seizure is regarded as acute symptomatic and may be recurrent or present as SE. Late seizures are defined as those that occur more than seven days after stroke. This type of seizure is also known as unprovoked seizure. Many definitions were applied in different studies, but most of them confirmed that stroke was strongly associated with a high incidence of early seizures and epilepsy (Table 6).<sup>53-56</sup> The risk of subsequent unprovoked seizures was 33.0% among subjects with a first acute symptomatic seizure and 71.5% among individuals with a first unprovoked seizure.<sup>57</sup>

Seizures in stroke patients have specific clinical manifestations. Seizures may not be recognized by patients or witnesses, and the lack of awareness about this condition may be higher in older patients. Video-EEG monitoring is helpful to establish a definitive diagnosis in these cases.<sup>58,59</sup> Common seizures include partial seizures (early onset) and secondarily generalized tonic-clonic seizures (late onset).<sup>60</sup> Stroke is one of the major causes of SE. The mortality rate in a general population with SE (645 cases) was 17.8%.<sup>61</sup> The rate of SE-associated mortality in the elderly is 38%, which is the highest of any age group, and the rate in the very old elderly (age >80 years) is  $\geq 50\%$ .<sup>62</sup> The incidence of SE was 1.1% in a cohort of

**Table 6.** Incidence of seizure and epilepsy associated with stroke

Study	Early seizures	Epilepsy
Oxfordshire Community Stroke Project <sup>53</sup>		4.2% at 1 year 9.7% at 5 years
Rochester <sup>54</sup> (535 stroke patients): 23-fold higher risk in the first year 17-fold higher risk of recurrent seizures	6% (78% within 24 hours)	3% at 1 year 4.7% at 2 years 7.4% at 5 years 8.9% at 10 years
Northern Manhattan <sup>55</sup>	4.1%	
Greater Cincinnati <sup>56</sup>	3.1% within 24 hours	

adults with first stroke residing in northern Manhattan<sup>55</sup> and 3% in a hospitalized population.<sup>48</sup> The first manifestation of stroke can be SE. Seizures are also common after intracerebral hemorrhage and may be nonconvulsive.<sup>63</sup>

The presumed mechanism of early seizures is a regional metabolic dysfunction leading to the release of excitotoxic neurotransmitters. The resulting accumulation of calcium and sodium might result in the depolarization of cellular membranes.<sup>48,64</sup> The causes of late-onset seizures may be structural changes, including gliosis, meningocerebral scarring, selective neuronal loss, deafferentiation, and collateral sprouting.

Cortical involvement and large lesions are strongly associated with the development of seizures and epilepsy.<sup>48,65</sup> Larger lesions with multilobar involvement are correlated with a higher incidence of seizures.<sup>66</sup> There is a strong association between lobar involvement and seizures after both ischemic and hemorrhagic stroke. In a prospective study, 15.4% of subjects with lobar or large intracerebral hemorrhage and 6.5% of subjects with cortical infarction had seizures.<sup>67</sup> Moreover, 8.5% of individuals with subarachnoid hemorrhage had seizures. Pre-hospital seizures were relatively more common in patients with subarachnoid hemorrhage.<sup>68</sup> The severity of the initial neurological deficit was a strong clinical predictor of seizures after ischemic stroke.<sup>48</sup> Although the harmful effect of post-stroke seizures on stroke outcomes remains controversial, many studies stressed this effect. Early seizures were associated with higher hospital mortality.<sup>68-71</sup> Delayed seizures at 30 days and 1 year after stroke were also correlated with higher mortality rates.<sup>48,69,70,72,73</sup> Moreover, a higher modified Rankin score at hospital discharge was associated with post-stroke seizures.<sup>38,60,63</sup> However, two prospective studies showed that early-onset seizures were not associated with a higher mortality rate<sup>56</sup> or worse neurological outcomes.<sup>57</sup> One case series suggested that the outcomes improved to a certain extent.<sup>56</sup>

Seizures are independently associated with an increased midline shift after intraparenchymal hemorrhage.<sup>63</sup> However, one study suggested that seizure was not an independent predictor of poor outcome and that it only reflected the more severe brain injury.<sup>73</sup> In addition, seizures might exacerbate preexisting neurological deficits.<sup>74,75</sup> Another study found that early-onset seizures after subarachnoid hemorrhage predicted the development of late seizures and poor outcomes.<sup>76</sup>

Early seizures in the penumbra zone, prolonged seizures, and SE can exacerbate neurological deficits, leading to poorer outcomes. There was a three-fold increase in mortality among patients with

generalized convulsive SE.<sup>77</sup>

Prophylactic AEDs are not necessary for patients with stroke.<sup>78,79</sup> In the case of a single acute seizure, other metabolic causes and precipitating factors should be identified before deciding on the treatment options. On many occasions, these events do not usually require AEDs. Most cases of single seizures are easily controlled using one AED.<sup>67,80,81</sup> However, AEDs should be used in situations involving a prolonged first acute seizure, acute recurrent seizures, or SE.<sup>82</sup> The early use of AEDs was not associated with a reduction in the risk of recurrent seizures after the discontinuation of these drugs.<sup>83</sup> This result can be explained by the fact that most AEDs are not anti-epileptogenic.

Late seizures can be managed using two approaches: waiting for a second late seizure that fits the definition of epilepsy or starting anti-epileptic therapy immediately. The decision can be made considering the patient's general condition and the severity and impact of the seizures. Therapy with AEDs should be started in cases of recurrent late seizures. Most epilepsy events associated with stroke have a favorable outcome after treatment with AEDs. A hospital-based observational study found that up to 67% of patients became seizure-free for at least 1 year,<sup>84,85</sup> and this outcome could usually be achieved using a single AED.

## Dementia and epilepsy

The prevalence of seizures in patients with dementia is high (range, 10-22%).<sup>86</sup> The mechanism of seizures in dementia is unclear. Excessive neuronal loss, including the loss of GABA interneurons, may be responsible for the generation of seizures. The establishment of a diagnosis is difficult in these cases. Even CPSs experienced by patients can be recognized as decreased or fluctuating brain function associated with dementia.<sup>87</sup> Epilepsy events may be undiagnosed in patients with dementia.

The following features suggest the presence of CPSs: short-term fluctuation or decrease in response and intermittent confusion. The cognitive decline caused by seizures can be prolonged in some cases. Repetitive symptoms can be a clue leading to a correct diagnosis. A few cases of nonconvulsive SE can mimic subacute dementia (epileptic subacute pseudodementia).<sup>18,88,89</sup>

An optimal quality of life for patients with dementia cannot be achieved without the proper diagnosis of coexisting epilepsy. Epilepsy can aggravate the general condition of these patients and worsen memory functions. A high level of suspicion is needed, and

the proper use of long-term video-EEG monitoring is necessary in cases of suspected epilepsy.

## Dose reduction in cases of decreased renal clearance

The dose of AEDs that are heavily metabolized or excreted through the kidney should be adjusted in elderly patients with decreased renal function to avoid the occurrence of dose-dependent adverse effects. These drugs include ethosuximide, gabapentin, pregabalin, levetiracetam, topiramate, and vigabatrin. The doses of these drugs may have to be reduced up to 50% in cases in which the GFR is decreased to 30-59 mL/min.<sup>90</sup>

## Conclusions

Epilepsy is common in the elderly. The establishment of a correct differential diagnosis between epilepsy and other seizure disorders that are common in the elderly is essential. The typical semiology of seizures in the elderly may be different from those observed in younger populations. AEDs that are suitable for the elderly should be selected considering drug pharmacokinetics, drug interactions, and possible adverse effects. There is a strong relationship between epilepsy and stroke or dementia.

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