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Pharmacological Treatment of Epilepsy in Elderly Patients

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The incidence and prevalence of epilepsy are highest in elderly people, and the etiologies of epilepsy in the elderly differ from those in other age groups. Moreover, diagnosing and treating epilepsy in elderly people may be challenging due to differences in clinical characteristics and physiological changes associated with aging. This review focuses on the pharmacological treatment of epilepsy in elderly patients.

Key Words epilepsy, elderly, treatment.

INTRODUCTION

The elderly population, which is usually defined as people aged ≥65 years,[1] is quite commonly affected by the neurological disease epilepsy.[2] The incidence and prevalence of epilepsy are highest in elderly people, being almost twofold higher those observed in children, and increasing with age. Moreover, the frequency of epilepsy in people aged >80 years is threefold higher that in children.[3] The number of elderly people is increasing with the aging of populations worldwide, which will lead to increases in the number of epilepsy cases among the elderly.[4]

The etiology of epilepsy in the elderly population differs from that in other age groups. Diagnosing epilepsy in the elderly is difficult due to the high prevalence of seizure-mimicking disorders such as syncope, transient global amnesia, transient ischemic attacks, and vertigo, as well as cognitive dysfunction.[5]

Selecting the appropriate antiepileptic drugs (AEDs) for treating epilepsy in elderly patients is an important issue since this population exhibits alterations in pharmacokinetic and pharmacodynamic parameters. Furthermore, the elderly population is prone to drug-drug interactions since they commonly take several medications for comorbid disorders.

This article reviews the etiology, diagnosis, and treatment of epilepsy in elderly patients.

ETIOLOGY

The etiologies of epilepsy in elderly patients are quite different from those in other age groups.

The most common etiologies of epilepsy in elderly patients are cerebrovascular disease, neurodegenerative disorders, brain tumor, and traumatic brain injury.[6] Moreover, metabolic insults and infection of the central nervous system can lead to seizures in the elderly.[7] However, the cause of approximately 50% of epilepsy cases among elderly patients remains unknown.[8]

Cerebrovascular diseases reportedly account for the etiology in 15–40% of epilepsy cases in elderly patients.[8-10] Seizures can occur due to cerebral infarction, subarachnoid hemorrhage, and intracerebral hemorrhage, with an association with hemorrhagic strokes being

more likely than one with cerebral infarction.[11,12] A meta-analysis demonstrated that early seizures, cortical involvement, and cerebral hemorrhage increase the risk of developing poststroke epilepsy. The epileptogenesis of poststroke scar is associated with enhanced neuronal excitability, as found in experimental models.[13] Hypertension (HTN) is a major risk factor for cerebrovascular diseases and the leukoaraiosis that are often encountered in epilepsy. HTN and leukoaraiosis may modulate seizure susceptibility, possibly via a contribution from the cerebral renin-angiotensin system.[14,15] Neurodegenerative disorders account for 10–20% of the etiology of epilepsy cases in elderly patients.[16,17] Elderly people with dementia reportedly have two- to tenfold increased risks of developing new-onset epilepsy.[6] Similar risks of developing epilepsy has been reported in patients with Alzheimer's disease and vascular dementia.[18] Brain tumors reportedly account for the etiology in 5–11.8% of epilepsy cases in elderly patients,[8,19] with 20–45% of patients with brain tumors developing seizures as an early symptom. The incidence of epilepsy in brain tumors varies with the type of malignancy. Epilepsy develops in 65–95% of patients with astrocytoma, oligodendroglioma, and meningioma, and in 15–25% of those with malignant gliomas.[20] Traumatic brain injury accounts for the etiology in up to 20% of epilepsy cases in elderly patients, and being aged >65 years is a risk factor for developing epilepsy after a head trauma.[21] Neuroimaging and neuropsychological tests are required to evaluate the etiologies of epilepsy in elderly patients.

DIAGNOSIS: DIFFERENT CLINICAL MANIFESTATIONS IN ELDERLY PATIENTS

There are several differences in the clinical manifestations of epilepsy between elderly and other adult patients. Focal seizure is the most common seizure type of epilepsy in elderly patients,[3] whereas generalized seizure is more common in other adult patients. Of the two subtypes of focal seizures, impaired awareness is commonplace in elderly patients while focal seizures with awareness.[9] Although epilepsy in elderly patients can manifest as generalized tonic-clonic seizure, the seizure in the majority of cases is more likely to be a previously unrecognized focal to bilateral tonic-clonic seizure.[22,23]

The clinical symptoms of focal seizure in elderly patients are significantly more diverse and atypical. Elderly patients are likely to have less-specific seizure symptomology and auras compared with young adult patients. Furthermore, despite the large proportion of focal impaired-awareness seizures in epilepsy among elderly patients, oroalimentary and hand automatism are not usually observed during seizure. Short-term dizziness and motionless staring followed by brief consciousness disturbance or confusion may be the only manifestations of focal impaired-awareness seizures in elderly patients.[22] Vague symptoms and lack of typical automatism make the diagnosis difficult, which can result in clinicians underdiagnosing such seizures. Moreover, the duration of postictal confusion is longer in elderly patients than in other adult patients, sometimes lasting for days or even weeks.[10] Elderly patients are more susceptible to injuries caused by seizures, and falls may also result in head injury or bone fracture.[10] In addition to the previously mentioned clinical characteristics, the incidence of status epilepticus (SE) is higher among elderly patients than in other age groups.[24] The mortality rate associated with SE varies with age, and is approximately 50% among individuals aged >80 years.[25]

MANAGEMENT

General considerations

The International League Against Epilepsy (ILAE) and the American Epilepsy Society/American Academy of Neurology (AES/AAN) recommended lamotrigine (LTG) and gabapentin (GBP) as efficacious monotherapies for newly diagnosed and untreated focal seizures based on strong evidence (Table 1).[26,27] However, there are no guidelines for elderly

Table 1. Guidelines of the ILAE and the AES/AAN for elderly patients with focal-onset seizures[26,27]

ILAE guidelines (2013)			AES/AAN guidelines (2018)
Type of seizures	Antiepileptic drugs	Level of evidence	
Newly diagnosed/ untreated focal-onset seizures in elderly	Lamotrigine, gabapentin	A	Lamotrigine (Level B)
	Carbamazepine	C	Gabapentin (Level C)
	Topiramate, valproate	D	
	Oxcarbazepine, levetiracetam, phenytoin, pregabalin, clonazepam, clobazam	E	
Generalized tonic-clonic seizures	No data	No data	No recommendation
Myoclonic seizures	No data	No data	No recommendation
Absence seizures	No data	No data	No recommendation

ILAE: International League against Epilepsy, AES/AAN: American Epilepsy Society/American Academy of Neurology.

patients with other types of seizures. Elderly patients are sensitive to the adverse effects of AEDs, and drug compliance in this population is affected more by the adverse effects of AEDs than by their efficacy. When initiating epilepsy treatments in elderly patients, it is necessary to consider the pharmacodynamic and pharmacokinetic parameters of AEDs, the comorbid disorders, and concomitant medical treatments. The clinical evidence indicates that newer AEDs for managing epilepsy in elderly patients are better than older AEDs due to their lower risks of adverse effects and drug-drug interactions.[28]

Pharmacological considerations

Aging is accompanied by several physiological changes. Physiological aging alters the pharmacodynamic and pharmacokinetic parameters of AEDs. The pharmacodynamic changes include decreases in the numbers and sensitivity of receptors and in the ability to maintain AEDs at stable levels. Therefore, the adverse effects of AEDs tend to be more severe in elderly patients than in other adult patients,[21] and so clinicians should prescribe AEDs using a "start low and go slow" regimen in elderly patients in order to minimize the risk of adverse effects. Pharmacokinetic changes also occur during the absorption, distribution, metabolism, and elimination of AEDs in the elderly. Renal clearance reduces with aging,[7] and so the dosage of AEDs should be adjusted according to creatinine clearance in elderly patients.[29] Several AEDs are metabolized by the liver. Since hepatic function also progressively decreases with aging, the consequent reduction in serum albumin leads to an increase in the free fraction of AEDs,[29] which increases the risk of adverse effects.

When a clinician is choosing an AED for an elderly patient, it is also important to consider the potential for drug interactions since many of these patients take other medications for comorbid diseases. Older AEDs such as enzyme inducers or inhibitors increase the likelihood of interactions with other medications. Carbamazepine (CBZ), phenytoin (PHT), and phenobarbital (PB) are enzyme inducers that can decrease the levels of concomitantly administered medications. The concentrations of oral anticoagulants, antidepressants, antimicrobials, psychotropic drugs, and cardiovascular drugs can be decreased by these enzyme-inducing AEDs. In contrast to enzyme inducers, valproate (VPA) is an enzyme inhibitor that will increase the concentration of concomitant drugs.[30] Newer AEDs with relatively few drug interactions, such as LTG and levetiracetam (LEV), might be more suitable for elderly patients on polypharmacy regimens.[9] AEDs with no significant pharmacokinetic interactions are suitable for elderly patients who take multiple medications to treat other diseases. Furthermore, AEDs without enzyme-inducing effects have the advantage of having fewer or no harmful effects on atherosclerosis development and bone metabolism.[31]

Efficacy and clinical evidence

Medication guidelines and recommendations can vary between countries. None of the newer AEDs have demonstrated superior efficacy to the older AEDs.[32] A few clinical trials have investigated epilepsy in elderly patients. The UK Lamotrigine Elderly Study Group conducted a double-blind, randomized trial comparing LTG and CBZ in 150 newly diagnosed elderly patients,[33] and demonstrated that the time to first seizure did not differ between LTG and CBZ treatments. Another study that compared CBZ, LTG, and GBP in 593 elderly patients with new-onset epilepsy found that the seizure-free rate did not differ significantly among these AEDs.[34] The ILAE assigned Level-A recommendations to LTG and GBP for use in elderly adults with focal-onset seizures, while CBZ received a Level-C recommendation.[26] According to the AES/AAN guideline, LTG (Level B) should and GBP (Level C) may be considered in patients aged ≥60 years with new-onset focal epilepsy.[27] A randomized, double-blind trial showed that the seizure-freedom rate did not differ significantly among CBZ, LTG, and LEV treatments.[35] In the Keppra vs. Older Monotherapy in Epilepsy Trial (KOMET) study, the time to first seizure was similar for LEV and CBZ or VPA treatments.[36] A recent meta-analysis found that the probability of seizure freedom was higher for LEV than for LTG and did not differ significantly between LEV and CBZ.[37]

No previous clinical study has investigated AED treatments in elderly patients in South Korea. An expert opinion survey was recently performed in South Korea to evaluate the preferences of epileptologists for AEDs in various clinical situations according to seizure types, special populations, and comorbid conditions.[38] The 42 South Korean epileptologists who completed the survey recommended LEV and LTG as the treatments of choice in elderly patients.

Tolerability

Complaints about the adverse effects of AEDs are more common in elderly patients.[8] The common adverse effects in the elderly are listed in Table 2.[7,28] A regimen involving newer AEDs is a better choice in elderly patients because of their better tolerability compared to older AEDs. In previous clinical trials, LTG exhibited lower rates of rashes and somnolence compared to CBZ,[33] and LTG and GBP demonstrated significantly higher retention rates due to fewer adverse events compared with CBZ.[34] However, the retention rates of LTG and a sustained-release formulation of CBZ were less prominent, which might be explained by different

Table 2. Common AEDs and their adverse effects in the elderly[7,28]

AEDs	Adverse effects
Phenytoin	Cognition impairment, cardiac conduction abnormalities, diplopia, nystagmus
Carbamazepine	Hyponatremia, cardiac conduction abnormalities, weight gain, rash
Valproate	Weight gain, tremor
Gabapentin	Weight gain
Pregabalin	Somnolence, weight gain
Lamotrigine	Rash
Levetiracetam	Mood abnormalties
Oxcarbazepine	Hyponatremia, cardiac conduction abnormalities, diplopia, rash
Topiramate	Cognition impairment, renal stone, glaucoma, weight loss
Zonisamide	Cognition impairment, renal stone, weight loss

AEDs: antiepileptic drugs.

formulas, release rates, and dosing rates.[39] In addition to LTG and GBP, LEV is a reasonable and safe choice for elderly patients.[40,41] A randomized, double-blind trial found that the 1-year treatment retention rate was higher for LEV than for controlled-release CBZ. The retention rate of LTG was similar to that of LEV, but it did not differ significantly from those of other drugs.[36] In the KOMET study, the time to treatment withdrawal was longer for LEV than for CBZ.[37]

Comorbid disorder and drug-drug interactions

The high prevalence of concomitant diseases in elderly patients makes it more likely that they will be taking multiple medications concurrently. This situation results in the incidence of adverse drug-drug interactions being very high in the elderly population.[42] A recent study found that 98% of patients with adverse drug reactions were on polypharmacy regimens.[43] Therefore, elderly patients with epilepsy need to be prescribed AEDs that do not interact with other medications or otherwise affect their comorbid medical disorders. Patients with cerebrovascular diseases—which is the most common etiology of epilepsy in elderly people—generally take several medications such as antiplatelets, antihypertensives, antiarrhythmic drugs, statins, and psychotropic agents.

Approximately half of elderly patients with epilepsy experience drug interactions,[44] with first-generation AEDs being most commonly linked to interactions with other drugs. First-generation enzyme-inducing AEDs such as PHT, PB, and CBZ decrease the plasma concentrations of old and new oral anticoagulants.[45,46] The newer AEDs such as GBP, LEV, pregabalin, and low-dosage LTG, which is associated with less-severe drug interactions, may be suitable alternative choices for minimizing drug interactions.[47-49] Although most of the second- and third-generation AEDs do not have enzyme-inducing effects, LEV decreases the effect of new oral anticoagulants by inducing P-glycoprotein.[45,46] In addition to the decreases in renal and hepatic metabolism, elderly people have increased prevalence rates of chronic kidney and liver diseases. Older AEDs are generally metabolized by the liver and bind strongly to albumin, thus potentially worsening comorbid liver disease or possibly increasing the toxicity of AEDs.[50] Reducing the dosage or changing to newer AEDs that are renally excreted, such as GBP, topiramate (TPM), or LEV, is an appropriate treatment strategy for patients with liver disease. The dosages of AEDs that are excreted by the kidney need to be adjusted appropriately in patients with kidney disease, and may also need to be increased after hemodialysis.[51] Lower dosages and slower titration rates are generally recommended in patients with both liver and kidney diseases.

Since cognitive impairment is common in the elderly population, AEDs with cognitive side effects (e.g., TPM and zonisamide) are not prioritized.[21] PHT and CBZ may affect atrioventricular conduction, and therefore clinicians should be cautious when applying these AEDs to treat patients with cardiac arrhythmias.[52] AEDs can also affect lipid profiles, with CBZ possibly increasing the levels of low- and high-density lipoproteins,[53] and oxcarbazepine, LEV, and TPM possibly also increasing the low-density-lipoprotein level.[54] Enzyme-inducing AEDs such as PHT and CBZ can decrease the level of vitamin D. VPA damages bones by directly suppressing osteoblasts,[55] but there is less evidence indicating whether newer AEDs impair bone health. Data regarding the impacts of LEV and TPM on bone health are conflicting. LTG administered as a monotherapy might not affect the bone density.[56]

SUMMARY AND RECOMMENDATIONS

The findings of this study and the resulting recommendations can be summarized as follows:

- Epilepsy in elderly patients has quite different etiology, clinical manifestations, and choice of AEDs compare with other adult patients.

- In addition to the efficacy of AEDs, their adverse effects and drug interactions as well as comorbid diseases and economic status must be considered when choosing AEDs for treating epilepsy in elderly patients.

- AEDs that are suitable for treating epilepsy in elderly patients have 1) no interactions with other medications or AEDs, 2) no or low protein binding, 3) good adverse-effect profiles, and 4) little effect on cognitive function.

- The Drug Committee of the Korean Epilepsy Society has recommended LTG or LEV as the treatment of choice for epilepsy in elderly patients.

Author Contributions

Conceptualization: all authors. Investigation: all authors. Writing—original draft: Jong-Geun Seo. Writing—review & editing: all authors.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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