Pharmacological Treatment of Epilepsy in Elderly Patients

Jong-Geun Seo¹, Yong Won Cho², Keun Tae Kim², Dong Wook Kim³, Kwang Ik Yang³, Soon-Tae Lee¹, Jung-Ick Byun¹, Young Joo No¹, Kyung Wook Kang³, Daeyoung Kim¹

on behalf of the Drug Committee of Korean Epilepsy Society

INTRODUCTION

The elderly population, which is usually defined as people aged ≥65 years, is quite commonly affected by the neurological disease epilepsy. 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.

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.

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.

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. Moreover, metabolic insults and infection of the central nervous system can lead to seizures in the elderly. However, the cause of approximately 50% of epilepsy cases among elderly patients remains unknown.

Cerebrovascular diseases reportedly account for the etiology in 15–40% of epilepsy cases in elderly patients. 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. A meta-
analysis demonstrated that early seizures, cortical involve-
ment, and cerebral hemorrhage increase the risk of develop-
ing poststroke epilepsy. The epileptogenesis of poststroke
scar is associated with enhanced neuronal excitability, as
found in experimental models. Hypertension (HTN) is a
major risk factor for cerebrovascular diseases and the leuko-
araiosis that are often encountered in epilepsy. HTN and leu-
koaraiosis may modulate seizure susceptibility, possibly via a
contribution from the cerebral renin-angiotensin system. Neurodegenerative disorders account for 10–20% of the eti-
ology of epilepsy cases in elderly patients. Elderly people
with dementia reportedly have two- to tenfold increased
risks of developing new-onset epilepsy. Similar risks of de-
veloping epilepsy has been reported in patients with Al-
zheimer’s disease and vascular dementia. Brain tumors re-
portedly account for the etiology in 5–11.8% of epilepsy
cases in elderly patients, 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. Traumatic brain
injury accounts for the etiology in up to 20% of epilepsy cas-
es in elderly patients, and being aged >65 years is a risk factor
for developing epilepsy after a head trauma. Neuroimaging
and neuropsychological tests are required to evaluate the eti-
ologies 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 sei-
zure is the most common seizure type of epilepsy in elderly
patients, 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. 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 previ-
souly unrecognized focal to bilateral tonic-clonic seizure.

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 epi-
lepsy among elderly patients, oromandibular and hand automa-
tism are not usually observed during seizure. Short-term dizzi-
ness and motionless staring followed by brief consciousness
disturbance or confusion may be the only manifestations of fo-
cal impaired-awareness seizures in elderly patients. 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 last-
ing for days or even weeks. Elderly patients are more suscep-
tible to injuries caused by seizures, and falls may also result in
head injury or bone fracture. In addition to the previously
mentioned clinical characteristics, the incidence of status epi-
lepticus (SE) is higher among elderly patients than in other age
groups. The mortality rate associated with SE varies with age,
and is approximately 50% among individuals aged >80 years.

### MANAGEMENT

#### General considerations

The International League Against Epilepsy (ILAE) and the
American Epilepsy Society/American Academy of Neurolo-

| Type of seizures | ILAE guidelines (2013) | AES/AAN guidelines (2018) |
|------------------|------------------------|--------------------------|
| New onset        | Lamotrigine, gabapentin| Lamotrigine (Level B)    |
| Seizures in elderly | Carbamazepine          | Gabapentin (Level C)     |
| Oxcarbazepine, levetiracetam, phenytoin, pregabalin, clonazepam | Topiramate, valproate | No recommendation |
| Generalized tonic-clonic seizures | No data | No data |
| Myoclonic seizures | No data | No recommendation |
| Absence seizures | 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,29 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,29 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
formsulas, release rates, and dosing rates. In addition to LTG and GBP, LEV is a reasonable and safe choice for elderly patients. 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. In the KOMET study, the time to treatment withdrawal was longer for LEV than for CBZ.

**Comorbid disorder and drug-drug interactions**
The high prevalence of comorbid 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. A recent study found that 98% of patients with adverse drug reactions were on polypharmacy regimens. 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, 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. 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. 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. 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. 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. 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. PHT and CBZ may affect atrioventricular conduction, and therefore clinicians should be cautious when applying these AEDs to treat patients with cardiac arrhythmias. AEDs can also affect lipid profiles, with CBZ possibly increasing the levels of low- and high-density lipoproteins, and oxcarbazepine, LEV, and TPM possibly also increasing the low-density-lipoprotein level. Enzyme-inducing AEDs such as PHT and CBZ can decrease the level of vitamin D. VPA damages bones by directly suppressing osteoblasts, 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.

**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 compared 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.

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**Table 2. Common AEDs and their adverse effects in the elderly**

| 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 abnormalities                                    |
| 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.
Author Contributions

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

ORCID IDs

Jong-Geun Seo https://orcid.org/0000-0002-3944-5731
Yong Won Cho https://orcid.org/0000-0002-6127-1045
Keun Tae Kim https://orcid.org/0000-0002-7124-0736
Dong Wook Kim https://orcid.org/0000-0003-4484-0602
Kwang Ik Yang https://orcid.org/0000-0003-4767-7564
Jung-Ick Byun https://orcid.org/0000-0002-6224-4575
Young Joo No https://orcid.org/0000-0001-9362-8670
Daeyeong Kim https://orcid.org/0000-0001-9056-0017

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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REFERENCES

1. Orimo H. Reviewing the definition of elderly. Nihon Ronen Igakkai Zasshi 2006;43:27-34.
2. Chen LA, Cheng SJ, Jou SB. Epilepsy in the elderly. Int J Gerontol 2012;6:63-67.
3. Brodie MJ, Kwan P. Epilepsy in elderly people. BMJ 2005;331:1317-1322.
4. Stephen LJ, Brodie MJ. Epilepsy in elderly people. Lancet 2000;355:1441-1446.
5. Acharya VN, Acharya VV. Epilepsy in the elderly: special considerations and challenges. Ann Indian Acad Neurol 2014;17(Suppl 1):S18-S26.
6. Pugh MJ, Knoefel JE, Mortensen EM, Amuan ME, Berlowitz DR, Van Cott AC. New-onset epilepsy risk factors in older veterans. J Am Geriatr Soc 2009;57:237-242.
7. Lee SK. Epilepsy in the elderly: treatment and consideration of comorbid diseases. J Epilepsy Res 2019;9:27-35.
8. Tanaka A, Akamatsu N, Shouzaki T, Toyota T, Yamano M, Nakagawa M, et al. Clinical characteristics and treatment responses in new-onset epilepsy in the elderly. Seizure 2013;22:772-775.
9. Ramsay RE, Rowan AJ, Pryor FM. Special considerations in treating the elderly patient with epilepsy. Neurology 2004;62:524-529.
10. Choyd J, Hauser W, Towne A, Ramsay R, Mattson R, Gillam F, et al. Epidemiological and medical aspects of epilepsy in the elderly. Epilepsy Res 2006;68 Suppl 1:S39-S48.
11. Benbír G, Ince B, Bozhulcay M. The epidemiology of post-stroke epilepsy according to stroke subtypes. Acta Neurol Scand 2006;114:8-12.
12. Bladin CF, Alexandrov AV, Bellavance A, Bornstein N, Chambers B, Coté R, et al. Seizures after stroke: a prospective multicenter study. Arch Neurol 2000;57:1617-1622.
13. Ferlazzo E, Gasparini S, Beghi E, Sueri C, Russo E, Leo A, et al. Epilepsy in cerebrovascular diseases: review of experimental and clinical data with meta-analysis of risk factors. Epilepsia 2016;57:1205-1214.
14. Gasparini S, Ferlazzo E, Sueri C, Bianchi V, Ascoli M, Cavalli SM, et al. Hypertension, seizures, and epilepsy: a review on pathophysiology and management. Neurol Sci 2019;40:1775-1783.
15. Gasparini S, Ferlazzo E, Beghi E, Sofia V, Mumoli L, Labate A, et al. Epilepsy associated with leukoaraiosis mainly affects temporal lobe: a casual or causal relationship? Epilepsy Res 2015;109:1-8.
16. Martin RC, Faught E, Richman J, Funkhouser E, Kim Y, Clements K, et al. Psychiatric and neurologic risk factors for incident cases of new-onset epilepsy in older adults: data from U.S. Medicare beneficiaries. Epilepsia 2014;55:1120-1127.
17. Mendez M, Lim G. Seizures in elderly patients with dementia: epidemiology and management. Drugs Aging 2003;20:791-803.
18. Infeld P, Bodmer M, Schuerch M, Jack SS, Meier CR. Seizures in patients with Alzheimer's disease or vascular dementia: a population-based nested case-control analysis. Epilepsia 2013;54:700-707.
19. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. Neuro Oncol 2019;21:v1-v100.
20. Kargiotis O, Markoula S, Kyriasis AP. Epilepsy in the cancer patient. Cancer Chemother Pharmacol 2011;67:489-501.
21. Brodie MJ, Elder AT, Kwan P. Epilepsy in later life. Lancet Neurol 2009;8:1019-1030.
22. Collins NS, Shapiro RA, Ramsay RE. Elders with epilepsy. Med Clin North Am 2006;90:945-966.
23. Bergey GK. Initial treatment of epilepsy: special issues in treating the elderly. Neurology 2004;63:540-548.
24. Rohracher A, Reiter DP, Brigo F, Kalss G, Thomschewski A, Novak H, et al. Status epilepticus in the elderly—a retrospective study on 120 patients. Epilepsia 2016;127:317-323.
25. Leppik IE. Status epilepticus in the elderly. Epilepsia 2018;59 Suppl 2:140-143.
26. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kalviainen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2013;54:551-563.
27. Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JE, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy: report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Epilepsy Curr 2018;18:269-278.
28. Kaur U, Chauhan I, Gambhir IS, Chakrabarti S. Antiepileptic drug therapy in the elderly: a clinical pharmacological review. Acta Neurol Belg 2019;119:163-173.
29. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet 2013;52:627-645.
30. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol 2006;61:246-255.
31. Chuang YC, Chuang HY, Lin TK, Chang CC, Lu CH, Chang WN, et al. Effects of long-term antiepileptic drug monotherapy on vascular risk factors and atherosclerosis. Epilepsia 2012;53:120-128.
32. Kwan P, Brodie MJ. Clinical trials of antiepileptic medications in newly diagnosed patients with epilepsy. Neurology 2003;60:S2-S12.
33. Brodie MJ, Oversell PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine among elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. Epilepsy Res 1999;37:81-87.
34. Rowan AJ, Ramsay RE, Collins JM, Pryor F, Boardman KD, Uthman BM, et al. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. Neurology 2005;64:1868-1873.
35. Werhahn KJ, Trinka E, Dobesberger J, Unterberger I, Baum P, Deckert-Schmitz M, et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. Epilepsia 2015;56:450-459.
36. Pohlmann-Eden B, Marson AG, Noack-Rink M, Ramirez F, Tofighy A, Werhahn KJ, et al. Comparative effectiveness of levetiracetam, valproate and carbamazepine among elderly patients with newly diagnosed epilepsy: subgroup analysis of the randomized, unblinded KOMET study. BMC Neurol 2016;16:149.
37. Lenza G, Gore G, Josephson CB, Cree S, Jette N, Keezer MR. The medical treatment of epilepsy in the elderly: a systematic review and
38. Byun JI, Kim DW, Kim KT, Yang KI, Lee ST, Seo JG, et al. Treatment of epilepsy in adults: expert opinion in South Korea. *Epilepsy Behav* 2020;105:106942.

39. Saetre E, Perucca E, Isojärvi J, Gjerstad L; LAM 40089 Study Group. An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. *Epilepsia* 2007;48:1292-1302.

40. Ferrendelli JA, French J, Leppik I, Morrell MJ, Herbeuval A, Han J, et al. Use of levetiracetam in a population of patients aged 65 years and older: a subset analysis of the KEEPER trial. *Epilepsy Behav* 2003;4:702-709.

41. Alsaadi TM, Koopmans S, Apperson M, Farias S. Levetiracetam monotherapy for elderly patients with epilepsy. *Seizure* 2004;13:58-60.

42. Trinka E. Epilepsy: comorbidity in the elderly. *Acta Neurol Scand Suppl* 2003;180:33-36.

43. Kaur U, Chakrabarti SS, Singh B, Gambhir IS. A prospective observational pilot study of adverse drug reactions in patients admitted in the geriatric ward of a tertiary hospital in North India. *Curr Pharmacogenomics Person Med* 2018;16:147-155.

44. Pugh MJ, Vancott AC, Steinman MA, Mortensen EM, Amuan ME, Wang CP, et al. Choice of initial antiepileptic drug for older veterans: possible pharmacokinetic drug interactions with existing medications. *J Am Geriatr Soc* 2010;58:465-471.

45. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disord* 2014;16:409-431.

46. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Destrège L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;39:1330-1393.

47. Diaz RA, Sancho J, Serratosa J. Antiepileptic drug interactions. *Neurologist* 2008;14:555-565.

48. Ryvlin P, Montavont A, Nighoghossian N. Optimizing therapy of seizures in stroke patients. *Neurology* 2006;67:S3-59.

49. Mintzer S, Mattson RT. Should enzyme-inducing antiepileptic drugs be considered first-line agents? *Epilepsia* 2009;50 Suppl 8:42-50.

50. Boggs JG. Seizure management in the setting of hepatic disease. *Curr Treat Options Neurol* 2011;13:333-345.

51. Lacerda G, Krummel T, Saboury C, Ryvlin P, Hirsch E. Optimizing therapy of seizures in patients with renal or hepatic dysfunction. *Neurology* 2006;67:528-533.

52. Stefan H. Epilepsy in the elderly: facts and challenges. *Acta Neurol Scand* 2011;124:223-237.

53. Svalheim S, Luef G, Rauchenzauner M, Mørkrid L, Gjerstad L, Taubøll E. Cardiovascular risk factors in epilepsy patients taking levetiracetam, carbamazepine or lamotrigine. *Acta Neurol Scand Suppl* 2010;30-33.

54. Kim DW, Lee SY, Shon YM, Kim JH. Effects of new antiepileptic drugs on circulatory markers for vascular risk in patients with newly diagnosed epilepsy. *Epilepsia* 2013;54:e146-e149.

55. Petty SJ, O’Brien TJ, Wark JD. Anti-epileptic medication and bone health. *Osteoporos Int* 2007;18:129-142.

56. Sheth RD, Hermann BP. Bone mineral density with lamotrigine monotherapy for epilepsy. *Pediatr Neurol* 2007;37:250-254.