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# Antiepileptic pharmacotherapy in old age: evidence-based approach versus clinical routine – English Version

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## Abstract

With respect to epilepsy in old age, two groups of patients with different needs and challenges must be distinguished, which are also treated separately in this article: those who have grown old with epilepsy and those with epilepsy occurring for the first time in older age. Diagnostically, the first group is unproblematic as there are only relatively rarely patients with a misdiagnosis of epilepsy that has been maintained over decades. In contrast, epilepsy beginning in older age is more often misdiagnosed or diagnosed with a delay because of the often comparatively harmless semiology including nonconvulsive status epilepticus. Therapeutically, the question of switching from an "old" antiepileptic drug with negative effects on electrolytes, hormones, bone density, hepatic and vitamin metabolism as well as on cognitive parameters, such as alertness and memory, to a "modern" agent frequently arises. While many of these newer compounds offer benefits there are always surprises with unexpected, particularly psychiatric, adverse effects. If the patient has been seizure-free for a long time, the question of discontinuing or at least reducing the dose of antiepileptic drugs naturally arises. At the onset of epilepsy in old age, the selection of an antiepileptic drug, which usually needs to be taken for the rest of the patient's life, requires special consideration of individual aspects, not least because of the often numerous comorbidities and already existing medications. The aim of this article is to present the current state of knowledge and to assist in the care of older patients in the area of conflict between the limited evidence-based data and the necessity of a therapeutic decision in routine clinical practice.

**Keywords**
Antiseizure medication · Adverse events · Efficacy · Elderly patient · Seizure freedom

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Epilepsy is often considered a lifelong condition; given that mortality is not relevantly increased, many patients grow old with their epilepsy. This then requires an adjustment to antiepileptic therapy over the years, either in the choice of antiepileptic drugs or in a reduction of the previous dose. The incidence of epileptic seizures and epilepsy shows a U-shaped course, increasing significantly after the age of 60; the most common causes include cerebrovascular and neurodegenerative changes. These age-related epilepsy syndromes are sometimes a diagnostic challenge, but many patients respond well to antiepileptic drugs.

## The aging patient

When patients acquire epilepsy in childhood or early to mid-adulthood, the question arises after a few years and even more

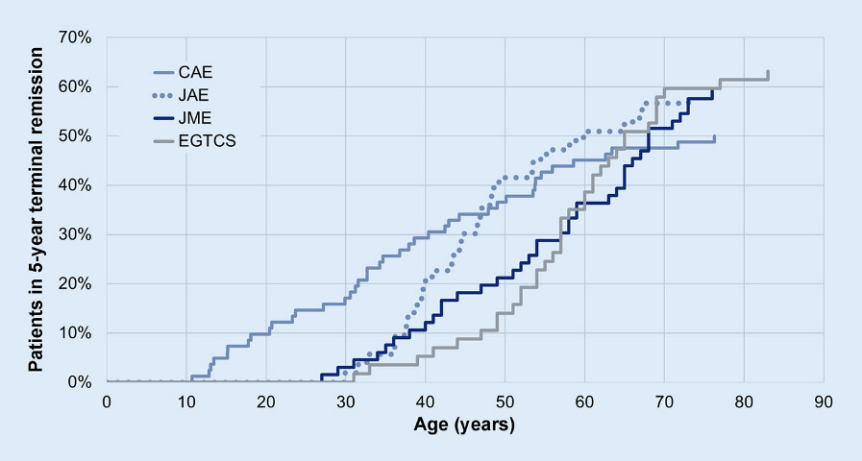


**Fig. 1** ▲ Proportion of patients with genetic generalized epilepsy with 5-year terminal remission of seizures depending on age. An almost linear relationship is shown for all four syndromes. Beyond the age of 65 years, more than 40–50% of patients were free of epileptic seizures in the last 5 years. The data are based on the results of studies [24, 25, 63]. *CAE* childhood absence epilepsy, *JAE* juvenile absence epilepsy, *JME* juvenile myoclonic epilepsy, *EGTCS* epilepsy with generalized tonic-clonic epilepsy only. (Many thanks go to Dr. Bernd Vorderwülbecke for preparing the figure)

so with increasing age whether—if patients remain seizure-free—antiepileptic medication still needs to be taken. To answer this question, data from epidemiological studies on the natural course of epilepsy and the risk of recurrence after discontinuation of antiepileptic drugs need to be considered. Even if—despite freedom from seizures or in the absence of freedom from seizures—antiepileptic drugs are not (or cannot be) discontinued, it must be considered, especially in the aging patient, whether the risk of adverse drug effects when taking older substances can be minimized by switching to a newer antiepileptic drug or generally by reducing the daily dose.

There are virtually no studies on the aforementioned points specifically for older patients with long-standing disease. The following discusses some of the data that at least take into account the aspect of patient age or epilepsy duration and, thus, can be partially extrapolated to the aging patient.

## Natural history of epilepsy

Methodologically, a distinction needs to be made between incidence and prevalence cohorts. The former includes patients at the onset of epilepsy and follows the course of the disease prospectively over the subsequent years or decades. The latter retrospectively examines the course of epilepsy at a defined point in time. Incidence cohorts are methodologically superior, but provide results only after a long latency; in addition, classification definitions may change over longer periods of time, making interpretation of results difficult.

In Finland, a cohort of 102 children with new-onset epilepsy was put together in the 1970s. After almost 45 years (median), more than 80% of the patients were seizure-free in the last year, and 81% of these seizure-free patients were no longer taking antiepileptic medication [54]. Patients with "idiopathic or cryptogenic" epilepsy—according to the classification at that time—were significantly more often seizure-free than those with "symptomatic" epilepsy.

The best known incidence cohort is the British National General Practice Study of Epilepsy, which in the 1980s included 564 patients with epilepsy; over 60% of patients had "idiopathic or cryptogenic" epilepsy, in line with the classification of the Finnish study [52]. After 9 years, 84% of patients were seizure-free in the last year, and 87% of patients were no longer taking an antiepileptic drug [11].

A multicenter study from Italy assessed more than 1000 children and adults with epilepsy in a prevalence cohort; 86% of patients were younger than 45 years, and median follow-up was 16 years [5]. In 77% of patients, 5-year remission was observed; predictors included genetic generalized epilepsy.

Although the two studies with incidence cohorts and the Italian prevalence cohort show a generally favorable seizure prognosis in epilepsy in the long term, and thus with increasing age, they do not specifically answer the question of how early-onset epilepsy presents explicitly in older age.

More reliable data are available for genetic generalized epilepsies; the Berlin epilepsy group has been able to analyze disease courses into old age based on the well-documented medical records from the "Janz archive." For the four generalized epilepsy syndromes that can persist into adulthood, there was an almost linear relationship between the age of patients and the probability of having been seizure-free in the preceding 5 years (**Fig. 1**).

## Discontinuation of antiepileptic drugs

Two studies prospectively randomized the effect of antiepileptic drug discontinuation on the risk of seizure recurrence; in both studies, patients were previously seizure-free for 2 years. In a study of more than 1000 patients, 41% of patients had seizure recurrence 2 years after discontinuation, compared to a rate of 22% in patients that continued to take an antiepileptic drug [37]. The longer patients were seizure-free, the more likely they were to have no seizure recurrence after stopping the antiepileptic drug. In the second study, 12 months after discontinuation, 15% of 79 patients experienced a recurrence, compared to 7% of 81 patients that continued treatment [34].

In a meta-analysis of nearly 1800 patients (median age 15 years) from 10 prospective and retrospective studies, 46% of patients experienced seizure recurrence 5 years (median) after antiepileptic drug discontinuation [28]. A number of predictors of seizure recurrence have been identified, including once again, the duration of seizure freedom before antiepileptic drug discontinuation. This predictor was also shown in a study from the Berlin working group in 84 patients with genetic

generalized epilepsy; when patients were seizure-free for less than 5 years before discontinuation, two-thirds had a recurrence, whereas when patients were seizure-free for longer, only one in three had a recurrence [62]. Since older age is associated with a greater likelihood of longer terminal seizure freedom in genetic generalized epilepsy, it is reasonable to assume that in older patients, discontinuation of the antiepileptic drug is associated with a lower risk of seizure recurrence compared with younger patients.

However, the decision to discontinue an antiepileptic drug—in both younger and older patients—is always a highly individual one that must take into account the patient's current life situation and their personal concerns about seizure recurrence or the risks of drug continuation. The discussion about discontinuing an antiepileptic drug should be conducted within the framework of shared decision-making between physician and patient and, if necessary, relatives.

## Reducing the adverse effects of antiepileptic drugs

Older patients with epilepsy since childhood or early adulthood have sometimes been treated for decades with older antiepileptic drugs such as phenobarbital, primidone, phenytoin, or carbamazepine. In general, these agents cause more adverse effects than newer antiepileptic drugs, including subjectively experienced side effects such as fatigue and cognitive impairment, decreased bone density with greater fracture risk [27], and metabolic laboratory abnormalities in the form of increased lipid levels with an increased risk of cardiovascular events. A prospective study (albeit one not focused on elderly patients) showed that switching from carbamazepine or phenytoin to lamotrigine or levetiracetam resulted in a significant reduction in atherogenic cholesterol and triglycerides [40]. Therefore, especially in older patients, it is relevant to consider in the consultation the side effect spectrum of the aforementioned older antiepileptic drugs. However, in seizure-free patients, there is always a risk that a well-intended switch of an older antiepileptic drug to a newer one will lead to seizure recurrence. Especially in older patients that have been seizure-free for many years, a change of antiepileptic drugs should be thought through well and discussed with the patient or their relatives (shared decision-making). Clinical practice shows that most seizure-free patients—if the antiepileptic drug cannot or should not be discontinued—do not wish to change their medication.

To avoid or minimize adverse effects of antiepileptic drugs in the aging patient, a reduction of the daily dose should be considered—both in seizure-free and non-seizure-free patients. Although there are no specific studies on this, about two thirds of the dose prescribed for younger patients is sufficient for most older patients due to reduced hepatic and renal function.

## New-onset epilepsy in older patients

New-onset seizures and epilepsy in older age pose a particular challenge due to the often preexisting comorbidities and causative damage, and also due to the fact that they can lead to an additional relevant restriction in quality of life and independence. Therefore, special care is required in establishing the indication and implementing drug treatment with antiepileptic drugs, and tolerability aspects are particularly important [2]. The aim is both to avoid unnecessary pharmacotherapies and to select and adapt any necessary treatment on a patient-specific basis.

The following information refers almost exclusively to monotherapies in the initial treatment of epilepsy with onset in older age. A presentation of the multitude of possible combination therapies would go beyond the scope of this article.

## Primary prevention

### Epileptic seizures and epilepsy

Precautionary administration of antiepileptic drugs in older age is generally not advisable, even in the presence of diseases known to be risk factors for epileptic seizures and epilepsy, such as diffuse cerebral circulatory disorders and proliferative or degenerative central nervous system (CNS) disorders. Guidelines from the European Stroke Organization for the management of epileptic seizures and post-stroke epilepsy have argued against this [23]. A recent Cochrane Review analyzed two randomized double-blind studies [8]. However, the first trial compared valproic acid and placebo administration for up to 1 year in only 72 patients after intracerebral hemorrhage and found no significant difference in the risk of subsequent epileptic seizures. In the second study, 784 adults with acute stroke were treated with diazepam or placebo for 3 days. Again, no difference was found in the risk of epileptic seizures at 3 months after either hemorrhagic or ischemic insults. Having said that, in a subgroup analysis of cortical infarcts in the carotid stromal area, primary prevention with diazepam was associated with a significantly lower risk of seizures.

This should stimulate further prospective double-blind studies with temporary administration of antiepileptic drugs or other agents, such as statins, which have already been shown to reduce the incidence of both early seizures and epilepsy after stroke [1, 68]. In planning appropriate studies and patient selection, it may help that it has recently been shown that the detection of epileptiform electroencephalography activity in the first week is a significant predictor of post-stroke epilepsy [47].

Furthermore, it is reasonable and desirable to treat known and treatable risk factors for the occurrence of cerebrovascular and also degenerative brain diseases. This is especially true not only for arterial hypertension [56] but also for atrial fibrillation [42] and other cardiac arrhythmias as well as diabetes mellitus [3].

Even in patients with newly diagnosed brain tumors who have not yet had epileptic seizures, two randomized trials failed to demonstrate any benefit for primary prevention [17, 22]. Thus, according to current recommendations of the Society for Neuro-Oncology and the European Association of Neuro-Oncology, primary prevention with antiepileptic drugs should not be given [64], not even perioperatively [64, 65].

In neurodegenerative diseases such as Alzheimer's disease, the third most common cause of epilepsy in older age [59], there is also no evidence of benefit from primary prevention.

The other, relatively rare causes of epilepsy manifesting for the first time in old age, such as metabolic–toxic diseases, traumatic brain injury, or bacterial–viral CNS diseases, cannot be discussed in more detail here due to a lack of space; autoimmune epilepsy, which is increasingly important not least in old age, as well as the treatment of status epilepticus in old age, are discussed in separate articles of this focus issue [57, 61].

### Cardiovascular diseases

It is well established that an initial onset of epileptic seizures in older age is also an indicator of risk for subsequent vascular disorders such as myocardial infarction [26, 44, 67] or cerebral infarction [7, 10] due to the frequent vascular comorbidities and etiology. Therefore, all patients who are not already under suitable care should undergo an appropriate cardiologic and cerebrovascular work-up and, if necessary, medical or vascular surgical therapy in a timely manner.

## Secondary prevention

Acute symptomatic or early seizures after a stroke or other cerebral dysfunction or damage are by definition not epilepsy and, therefore, not an indication for long-term administration of antiepileptic drugs. If antiepileptic drugs were administered in the acute care hospital, they should either be discontinued before transfer to a rehabilitation hospital or a specific recommendation for discontinuation should be given within the subsequent few weeks. This is often not the case in everyday clinical practice in German-speaking countries as well as internationally [48], but it should be observed without fail [23].

By contrast, the 10-year risk of recurrence after an initial unprovoked epileptic seizure ("late seizure") following structural cerebral damage is more than 60%, which, according to the 2014 International League Against Epilepsy (ILAE) definition of epilepsy, means that the diagnosis of epilepsy is already made after one seizure [16] and the initiation of pharmacotherapy is usually justified. To more accurately and individually predict the likelihood of recurrence of further seizures depending on factors such as age, duration of hospitalization in the acute care hospital, early seizures, or vascular risk factors, different models and scales for risk at 1 year [9, 58] or at 5 years [20] have been developed and validated. In this context, it is also interesting that it was recently possible to confirm the assumption that recanalization therapies such as intravenous lysis therapy or mechanical catheter thrombectomy have no effect either on the occurrence of acute symptomatic (early) seizures or post-stroke epilepsy [69].

In tumor-related epilepsy with initial onset in older age, the indication for antiepileptic medication after the occurrence of a first seizure is usually out of the question, even though there are major differences with regard to the risk of recurrence depending on the type, size, and localization of the mass [45].

By contrast, in Alzheimer's disease or other forms of dementia, there is no justification for a diagnosis of epilepsy after a first unprovoked seizure in older age, since the 5-year recurrence risk for further seizures is only 32% and not different from that in controls of previously seizure-free patients (33%; [35]).

### Results of randomized trials

A number of clinical studies are available on the treatment of epilepsy that first begins in older age, including only four accessible published double-blind randomized studies involving initial treatment with monotherapy specifically in older age and a subgroup analysis of older patients from an adult study (for another such study, the authors are only aware of one reference, but it was not accessible to them even as an abstract [41]). The remaining studies are in part open randomized trials, subgroup analyses, or retrospective evaluations of patient collectives, clinical observations, as well as systematic reviews and meta-analyses.

**Double-blind randomized trials.** The first double-blind randomized trial [6] was conducted in the United Kingdom (UK) and compared non-extended-release carbamazepine ($n = 48$) with lamotrigine ($n = 102$) in patients with a minimum age of 65 years. The study duration after reaching target doses was 24 weeks, and outcome parameters studied were seizure freedom and side-effect-related discontinuation rate. Lamotrigine was significantly superior to non-extended-release carbamazepine in terms of both the seizure freedom achieved (39% vs. 21%) and the discontinuation rate (29% vs. 58%; [6]).

The second three-arm double-blind randomized trial was conducted in the United States (US) in 593 patients with a minimum age of 65 years and a 1:1:1 allocation to lamotrigine, sustained-release carbamazepine, and gabapentin. With the same outcome parameters as in the UK study, the observation period was significantly longer at 1 year. In the US study, the seizure freedom achieved was slightly higher with sustained-release carbamazepine (71.4%) than with the other two agents (lamotrigine 61.3% and gabapentin 60%), but the discontinuation rate due to adverse events was, once again, significantly higher (31%) than with lamotrigine (12.1%) and gabapentin (21.6%; [50]).

The third double-blind randomized trial compared lamotrigine with sustained-release carbamazepine in 184 patients aged at least 65 years who had experienced a minimum of two unprovoked focal or bilateral tonic–clonic seizures in a 1:1 randomization. The study lasted 40 weeks and included a 4-week dose escalation to initial target doses of 100 mg lamotrigine or 400 mg extended-release carbamazepine per day, followed by a maintenance phase with the possibility of dosage adjustment depending on response. For the primary endpoint of retention in the trial, there was a slight, but not statistically significant, advantage for lamotrigine, 73% versus 67% with sustained-release carbamazepine. Conversely, for seizure freedom in the last 20 weeks of the study, there was a slight but also statistically nonsignificant advantage for extended-release carbamazepine with 57% for CBZ compared to 52% under lamotrigine [51].

The fourth and to date most recent randomized double-blind study specifically of initial onset of epilepsy in older age was conducted in Germany and Austria. It compared extended-release carbamazepine, lamotrigine, and levetiracetam at initial daily target doses of 400, 100,

and 1000 mg, respectively, for 58 weeks in 359 patients aged over 60 years with epilepsy according to the new ILAE definition ([16]; at least one late seizure) and with 1:1:1 randomization. Differences in seizure-free patients (extended-release carbamazepine 33.3%, lamotrigine 38.5%, and levetiracetam 42.6%) were without statistical significance. The discontinuation rate was significantly higher with extended-release carbamazepine (32.2%) compared to levetiracetam (17.2%) [66].

A subgroup analysis is available for lacosamide from a large randomized double-blind trial comparing it with sustained-release carbamazepine in adults [4]. Of the total of 886 patients, 119 were aged at least 65 years. Seizure-free rates at 6 months were minimally higher with carbamazepine ($n = 57$) than with lacosamide ($n = 62$), and less frequent adverse events and treatment discontinuations with lacosamide suggest a better tolerability profile than with sustained-release carbamazepine.

**Open randomized trials.** In a small open randomized trial of only 64 patients with post-stroke seizures, lamotrigine performed better than carbamazepine in terms of the seizure freedom achieved, but the difference just fell short of statistical significance [21]. Another open-label randomized trial compared levetiracetam ($n = 52$) and carbamazepine ($n = 54$) in post-stroke epilepsy. Levetiracetam had a nonsignificant advantage over carbamazepine in terms of the proportion of seizure-free patients, and the drug was better tolerated [13].

The manufacturer-sponsored KOMET (Keppra vs. Older Monotherapy in Epilepsy Trial) study was a retrospective subgroup analysis of 308 older patients aged at least 60 years from a comparative study with sustained-release carbamazepine, levetiracetam, and valproate. The primary endpoint was time to treatment discontinuation. This was longer with levetiracetam than with the other two agents, which was attributed to the more favorable tolerability profile of levetiracetam [46].

The SANAD-II trial, published in 2021, included only a few older patients with initial onset and treatment of focal epilepsy. In general, among a total of 990 predominantly adult patients with a follow-up of 2 years, seizure freedom at 12 months was found to be significantly higher with lamotrigine than with levetiracetam; no significant difference was found compared to zonisamide [36].

For epilepsy in the setting of Alzheimer's disease, the most common form of dementia in older age, only one open-label, small, three-arm randomized clinical trial with a total of 95 patients has been published [14]. Lamotrigine, levetiracetam, and phenobarbital were compared with a control group to assess cognitive effects of the antiepileptic drugs. A 4-week dose adjustment was followed by a 12-month assessment period. In terms of seizure freedom, there was no difference between the three antiepileptic drugs. However, there was an improvement in cognitive abilities under levetiracetam, whereas these deteriorated under lamotrigine and phenobarbital.

### Other open observations

A retrospective evaluation of the efficacy and tolerability of lacosamide ($n = 22$) and levetiracetam ($n = 24$) in the initial treatment of epilepsy in older adults showed seizure-free rates at 12 months of 73% and 71%, respectively [15].

A retrospective comparison of lacosamide ($n = 71$) and zonisamide ($n = 39$) in patients with a mean age at treatment initiation of 71 and 70 years, respectively, and often preexisting, refractory epilepsy, and a mean observation period of almost 2 years for lacosamide and almost 4 years for zonisamide showed seizure-free rates of 52% and 67%, respectively [53].

For eslicarbazepine acetate, a very small subgroup analysis of only 14 patients with a minimum age of 60 years in an open-label study of adults described a high side-effect-related discontinuation rate of 43% [43]. This poor tolerability was confirmed when compared to younger patients from the clinical trials and post-marketing data with approximately threefold more frequent treatment-related adverse events including hyponatremia [38].

### Systematic reviews and meta-analyses

A systematic review and meta-analysis described a higher probability of achieving seizure freedom for levetiracetam compared to lamotrigine and better tolerability or lower dropout probability for levetiracetam compared to carbamazepine [33]. Another study described the highest probability of achieving seizure freedom for lacosamide, lamotrigine, and levetiracetam in the absence of significant differences and a poor tolerability profile for sustained-release and non-extended-release carbamazepine, resulting in higher discontinuation rates compared to levetiracetam and valproic acid [32].

## Clinical routine

A Swedish study compared the retention rates of therapy with different antiepileptic drugs in 4991 patients with stroke-induced epilepsy between 2005 and 2010 [30]. The 5-year retention rates were highest for lamotrigine at 75% and levetiracetam at 69% and lowest for carbamazepine at 60% and phenytoin at 55%.

In a Japanese prospective multicenter cohort study, between 2014 and 2019, a total of 372 patients aged 64–81 years (approximately two-thirds men) receiving antiepileptic therapy for post-stroke epilepsy had their subsequent disease course assessed and the risk of seizure recurrence compared between patients receiving older- and newer-generation antiepileptic drugs [60]. Retention rates and tolerability were also recorded. The majority of patients ($n = 286$) were treated with newer agents, and only 36 with older-generation antiepileptic drugs and 50 with "mixed generation" agents. In both older- and newer-generation groups ($n = 322$), seizures recurred in 98 patients (30.4%), and 91 patients (28.3%) switched drugs during the follow-up period of more than 1 year. Recurrence of seizures was less frequent with newer-generation antiepileptic drugs than with older-generation antiepileptic drugs. Discontinuation of therapy and the need to change dosage were also less frequent with newer-generation agents.

## Current recommendations

Based on the studies presented to date and the authors' own clinical experience, the

following recommendations can be made for monotherapy in older patients:

- Lamotrigine should be given as a first-line agent.
- If the use of lamotrigine is not an option, gabapentin, lacosamide, levetiracetam, or zonisamide should be used; with eslicarbazepine acetate, care should be taken to avoid hyponatremia.
- In older patients with focal epilepsy, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramate, and valproic acid should not be used for initial monotherapy.
- Antiepileptic drug dosing should generally be slower and with lower target doses than in younger patients.

Austrian and Italian authors also recommend lacosamide and brivaracetam due to their low interaction risk and intravenous formulations for emergency situations or dysphagia; they see an advantage for preparations with the option of a formulation to be taken only once daily, such as eslicarbazepine acetate or perampanel [49].

Menon and Leppik [39], in a 2015 book chapter, surprisingly still give carbamazepine and phenytoin the same space as lamotrigine and levetiracetam (phenytoin is still used far more frequently in the US than in Europe), while Stefan and Hamer [55] also recommend zonisamide in addition to lamotrigine and levetiracetam due to the option of a single evening dose. A Swedish group of authors reminded readers of the documented efficacy and tolerability of gabapentin [12]. Lamotrigine and levetiracetam are also favored for epilepsy in the setting of dementia [18].

The justification for favoring lamotrigine and levetiracetam over carbamazepine is supported by a recent large Swedish study that showed lower mortality in post-stroke epilepsy for these two agents compared to carbamazepine [31]. The retrospective cohort study used data from multiple sources to collect data from 2577 patients with a median age of 78 years who had a stroke between 2005 and 2010 and subsequent onset of post-stroke epilepsy before the end of 2014. Compared to carbamazepine-treated patients, cardiovascular mortality was significantly lower with lamotrigine and levetiracetam.

This is also significant given that in 2020, the US Food and Drug Administration (FDA), citing in vitro findings, prompted a change in the labeling of lamotrigine to include a reference to antiarrhythmic activity, and recommended that lamotrigine be used for patients with cardiac conduction abnormalities (e.g., second- or third-degree heart block), ventricular arrhythmias, or cardiac disease/abnormalities (e.g., myocardial ischemia, heart failure, structural heart disease, Brugada syndrome, or other sodium channel diseases) to avoid lamotrigine [29]. An ad hoc task force of the ILAE and the American Epilepsy Society issued a statement qualifying this as a likely class effect of sodium channel blockers, but recommending that electrocardiogram leads be considered in patients over 60 years of age prior to initiation of treatment and that cardiac diagnostics also be initiated for abnormalities beyond nonspecific ST- and T-wave changes [19].

### Practical conclusion

- **As patients get older, antiseizure drugs should be critically reviewed for long-standing epilepsy.**
- **If seizure-free for more than 2 years, discontinuation of the antiseizure drug may be discussed.**
- **Switching from older to newer agents may be considered in order to minimize adverse effects; often the daily dose can be gradually reduced by one-third.**
- **Acute symptomatic seizures are not epilepsy and are not an indication for continuous antiepileptic medication.**
- **The first-line agent is lamotrigine (2 × 50 mg); if rapid seizure prevention needs to be established, bridging with levetiracetam (2 × 500 mg) may be used during the lamotrigine up-dosing phase.**
- **The occurrence of epileptic seizures or epilepsy at an advanced age should always prompt a cardiological and a cerebrovascular diagnostic work-up to exclude vascular stenoses and, if necessary, initiation of antiarrhythmic or antihypertensive therapy.**

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## Declarations

**Conflict of interest.** M. Holtkamp has received honoraria for consulting and lectures from Angelini/Arvelle, Bial, Desitin, Eisai, GW Pharma, UCB, and Zogenix from 2018 to 2022. He is coordinator of the guideline group "Management of First Epileptic Seizure and Epilepsies" of the German Neurological Society. He is also an associate member of the Drug Commission of the German Medical Association and advises the Federal Joint Committee on issues related to the pharmacological treatment of epileptic seizures and epilepsy. G. Krämer has received honoraria for consulting and lectures from Arvelle Therapeutics, GW Pharmaceuticals/Jazz Pharma, OM Pharma Suisse, Precisis, and Sandoz from 2018 to 2022. He is or has been a member of the German Neurological Society's guideline group on "Management of First Epileptic Seizure and Epilepsies" and the ILAE Task Force on Epilepsy in the Elderly (2017–2021).

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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## References

1. Acton EK, Khazaal O, Willis AW et al (2021) Statins for the prevention of post-stroke seizure and epilepsy development: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 30:106024
2. Arroyo S, Krämer G (2001) Treating epilepsy in the elderly: safety considerations. Drug Saf 24:991–1015
3. Baviera M, Roncaglioni MC, Tettamanti M et al (2017) Diabetes mellitus: a risk factor for seizures in the elderly—a population-based study. Acta Diabetol 54:863–870
4. Baulac M, Rosenow F, Toledo M et al (2017) Efficacy, safety, and tolerability of lacosamide monotherapy versus controlled-release carbamazepine in patients with newly diagnosed epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. Lancet Neurol 16:43–54
5. Beghi E, Beretta S, Carone D et al (2019) Prognostic patterns and predictors in epilepsy: a multicentre study (PRO-LONG). J Neurol Neurosurg Psychiatry 90:1276–1285
6. Brodie MJ, Overstall PW, Giorgi L, The UK Lamotrigine Elderly Study Group (1999) Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. Epilepsy Res 37:81–87
7. Chang CS, Liao CH, Lin CC et al (2014) Patients with epilepsy are at an increased risk of subsequent stroke: a population-based cohort study. Seizure 23:377–381

8. Chang RS, Leung WC, Vassallo M et al (2022) Antiepileptic drugs for the primary and secondary prevention of seizures after stroke. Cochrane Database Syst Rev 2:CD5398
9. Chi NF, Kuan YC, Huang YH et al (2018) Development and validation of risk score to estimate 1-year late poststroke epilepsy risk in ischemic stroke patients. Clin Epidemiol 10:1001–1011
10. Cleary P, Shorvon S, Tallis R (2004) Late-onset seizures as a predictor of subsequent stroke. Lancet 363(9416):1184–1186
11. Cockerell OC, Johnson AL, Sander JW et al (1995) Remission of epilepsy: results from the national general practice study of epilepsy. Lancet 346(8968):140–144
12. Compagno Strandberg M, Söderberg-Löfdal K, Kimland E et al (2020) Evidence-based anti-seizure monotherapy in newly diagnosed epilepsy: a new approach. Acta Neurol Scand 142:323–332
13. Consoli D, Bosco D, Postorino P et al (2012) Levetiracetam versus carbamazepine in patients with late poststroke seizures: a multicenter prospective randomized openlabel study (EpIC project). Cerebrovasc Dis 34:282–289
14. Cumbo E, Ligori LD (2010) Levetiracetam, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer's disease. Epilepsy Behav 17:461–466
15. Del Bianco C, Placidi F, Liguori C et al (2019) Long-term efficacy and safety of lacosamide and levetiracetam monotherapy in elderly patients with focal epilepsy: a retrospective study. Epilepsy Behav 94:178–182
16. Fisher RS, Acevedo C, Arzimanoglou A et al (2014) ILAE official report: a practical clinical definition of epilepsy. Epilepsia 55:475–482
17. Forsyth PA, Weaver S, Fulton D et al (2003) Prophylactic anticonvulsants in patients with brain tumour. Can J Neurol Sci 30:106–112
18. Frederiksen KS, Cooper C, Frisoni GB et al (2020) A European academy of neurology guideline on medical management issues in dementia. Eur J Neurol 27:1805–1820
19. French JA, Perucca E, Sander JW et al (2021) FDA safety warning on the cardiac effects of lamotrigine: an advisory from the ad hoc ILAE/AES task force. Epilepsia Open 6:45–48
20. Galovic M, Döhler N, Erdelyi-Canavese B et al (2018) Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. Lancet Neurol 17:143–152
21. Gilad R, Sadeh M, Rapoport A et al (2007) Monotherapy of lamotrigine versus carbamazepine in patients with poststroke seizure. Clin Neuropharmacol 30:189–195
22. Glantz MJ, Cole BF, Friedberg MH et al (1996) A randomized, blinded, placebo-controlled trial of divalproex sodium prophylaxis in adults with newly diagnosed brain tumors. Neurology 46:985–991
23. Holtkamp M, Beghi E, Benninger F, European Stroke Organisation et al (2017) European stroke organisation guidelines for the management of post-stroke seizures and epilepsy. Eur Stroke J 2:103–115
24. Holtkamp M, Janz D, Kirschbaum A (2018) Absence epilepsy beyond adolescence: an outcome analysis after 45 years of follow-up. J Neurol Neurosurg Psychiatry 89:603–610
25. Holtkamp M, Kowski AB, Merkle H, Janz D (2014) Long-term outcome in epilepsy with grand mal on awakening: forty years of follow-up. Ann Neurol 75:298–302
26. Janszky I, Hallqvist J, Tomson T et al (2009) Increased risk and worse prognosis of myocardial infarction in patients with prior hospitalization for epilepsy—the Stockholm heart epidemiology program. Brain 132:2798–2804
27. Krämer G (2005) Besondere Bedeutung von Knochenstoffwechselstörungen bei Epilepsien im höheren Lebensalter. Z Epileptol 18:184–187
28. Lamberink HJ, Otte WM, Geerts AT (2017) Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. Lancet Neurol 6:523–531
29. Lamictal (2021) US-amerikanische Verschreibungsinformationen. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Lamictal/pdf/LAMICTAL-PI-MG.PDF. Zugegriffen: 15. März 2022
30. Larsson D, Åsberg S, Kumlien E, Zelano J (2019) Retention rate of first antiepileptic drug in poststroke epilepsy: a nationwide study. Seizure 64:29–33
31. Larsson D, Baftiu A, Johannessen Landmark C et al (2022) Association between antiseizure drug monotherapy and mortality for patients with poststroke epilepsy. JAMA Neurol 79:169–175
32. Lattanzi S, Trinka E, Del Giovane C et al (2019) Antiepileptic drug monotherapy for epilepsy in the elderly: a systematic review and network meta-analysis. Epilepsia 60:2245–2254
33. Lezaic N, Gore G, Josephson CB et al (2019) The medical treatment of epilepsy in the elderly: a systematic review and meta-analysis. Epilepsia 60:1325–1340
34. Lossius MI, Hessen E, Mowinckel P et al (2008) Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus study). Epilepsia 49:455–463
35. Mahamud Z, Mononen CP, Brigo F et al (2020) Risk of epilepsy diagnosis after a first unprovoked seizure in dementia. Seizure 82:118–124
36. Marson A, Burnside G, Appleton R et al (2021) The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide, or lamotrigine for newly diagnosed focal epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Lancet 397(10282):1363–1374 (Erratum: Lancet 397(10287): 1808)
37. Medical Research Council Antiepileptic Drug Withdrawal Study Group (1991) Randomised study of antiepileptic drug withdrawal in patients in remission. Lancet 337(8751):1175–1180
38. Magalhães LM, Costa R, Vieira M et al (2021) Safety of eslicarbazepine acetate in elderly versus non-elderly patients with focal seizures: from pooled data of clinical studies to 8 years of post-marketing experience. Drug Saf 44:1099–1107
39. Menon U, Leppik IE (2015) Medical management of seizures in cerebrovascular disorders. In: Koubeissi MZ, Alshekhlee A, Mehndiratta P (eds) Seizures in cerebrovascular disorders. A clinical guide. Springer, New York—Heidelberg—Dordrecht—London, pp 121–132
40. Mintzer S, Skidmore CT, Abidin CJ (2009) Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. Ann Neurol 65:448–456
41. Motamedi M, Ghini M, Etemadi P, Ramim T (2013) Levetiracetam and lamotrigine in old aged onset of epilepsy: a randomized double blind clinical trial. Tehran Univ Med J 71:568–576
42. Naylor J, Churilov L, Johnstone B et al (2018) The association between atrial fibrillation and poststroke seizures is influenced by ethnicity and environmental factors. J Stroke Cerebrovasc Dis 27:2755–2760
43. Nielsen MK, Petrenaite V, Andersen NB (2017) Clinical experience with eslicarbazepine acetate in adults with sub-analysis of elderly. Seizure 53:94–99
44. Patorno E, Glynn RJ, Hernandez-Diaz S et al (2013) Risk of ischemic cerebrovascular and coronary events in adult users of anticonvulsant medications in routine care settings. J Am Heart Assoc 2:e208
45. Perucca E (2013) Optimizing antiepileptic drug treatment in tumoral epilepsy. Epilepsia 54(9):97–104
46. Pohlmann-Eden B, Marson AG, Noack-Rink M et al (2016) Comparative effectiveness of levetiracetam, valproate and carbamazepine among elderly patients with newly diagnosed epilepsy: subgroup analysis of the randomized, unblinded KOMET study. BMC Neurol 16:149
47. Punia V, Ellison L, Bena J et al (2022) Acute epileptiform abnormalities are the primary predictors of post-stroke epilepsy: a matched, case-control study. Ann Clin Transl Neurol. https://doi.org/10.1002/acn3.51534
48. Punia V, Honomichl R, Chandan P et al (2021) Long-term continuation of anti-seizure medications after acute stroke. Ann Clin Transl Neurol 8:1857–1866
49. Rohracher A, Kalss G, Kuchukhidze G et al (2021) New anti-seizure medication for elderly epilepsy patients—a critical narrative review. Expert Opin Pharmacother 22:621–634
50. Rowan AJ, Ramsay RE, Collins JF, VA Cooperative Study 428 Group et al (2005) New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. Neurology 64:1868–1873
51. Saetre E, Perucca E, Isojärvi J et al (2007) 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 48:1292–1302
52. Sander JW, Hart YM, Johnson AL, Shorvon SD (1990) National general practice study of epilepsy: newly diagnosed epileptic seizures in a general population. Lancet 336(8726):1267–1271
53. Sarkis RA, Nicolas J, Lee JW (2017) Tolerability of lacosamide or zonisamide in elderly patients with seizures. Seizure 49:1–4
54. Sillanpää M, Schmidt D (2009) Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy. Brain 132(4):989–998
55. Stefan H, Hamer H (2020) Ältere Patienten. In: Schmitt FC, Stefan H, Holtkamp M (eds) Epileptische Anfälle und Epilepsien im Erwachsenenalter: Diagnostik und Therapie. Springer, Berlin, pp 653–661
56. Stefanidou M, Himali JJ, Devinsky O et al (2022) Vascular risk factors as predictors of epilepsy in older age: the Framingham heart study. Epilepsia 63:237–243
57. Strzelczyk A (2022) Status epilepticus. Z Epileptol. In Vorbereitung
58. Strzelczyk A, Haag A, Raupach H et al (2010) Prospective evaluation of a post-stroke epilepsy risk scale. J Neurol 257:1322–1326
59. Tait L, Lopes MA, Stothart G et al (2021) A large-scale brain network mechanism for increased

seizure propensity in Alzheimer's disease. PLoS Comput Biol 17:e1009252
60. Tanaka T, Fukuma K, Abe S, PROPOSE Study Investigators et al (2021) Antiseizure medications for post-stroke epilepsy: a real-world prospective cohort study. Brain Behav 11:e2330
61. von Podewils F (2022) Ätiologien: Nicht nur vaskulär! (Immunologie). Z Epileptol. https://doi.org/10.1007/s10309-022-00488-7
62. Vorderwülbecke BJ, Kirschbaum A, Merkle H (2019) Discontinuing antiepileptic drugs in long-standing idiopathic generalised epilepsy. J Neurol 266:2554–2559
63. Vorderwülbecke BJ, Kowski AB, Kirschbaum A et al (2017) Long-term outcome in adolescent-onset generalized genetic epilepsies. Epilepsia 58:1244–1250
64. Walbert T, Harrison RA, Schiff D et al (2021) SNO and EANO practice guideline update: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Neuro Oncol 23:1835–1844
65. Wang X, Zheng X, Hu S et al (2019) Efficacy of perioperative anticonvulsant prophylaxis in seizure-naïve glioma patients: a meta-analysis. Clin Neurol Neurosurg 186:105529
66. Werhahn KJ, Trinka E, Dobesberger J et al (2015) A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. Epilepsia 56:450–459
67. Wilson DA, Wannamaker BB, Malek AM, Selassie AW (2018) Myocardial infarction after epilepsy onset: a population-based retrospective cohort study. Epilepsy Behav 88:181–188
68. Zhu Y, Gou H, Ma L et al (2021) Effects of double-dose statin therapy for the prevention of post-stroke epilepsy: a prospective clinical study. Seizure 88:138–142
69. Zöllner JP, Schmitt FC, Rosenow F et al (2021) Seizures and epilepsy in patients with ischaemic stroke. Neurol Res Pract 3:63