REVIEW ARTICLE

Epilepsy in the Elderly

Konrad J. Werhahn

SUMMARY

Background: Epilepsy is the third most common disease affecting the brain in the elderly. Current demographic trends will lead to an increased prevalence of epilepsy in the general population.

Method: A selective literature search revealed 102 relevant publications as of September 2008, 50 of which were original articles.

Results: The level of evidence was found to be very low. No guidelines, systematic reviews or meta-analyses are available, and there have been only three randomized, double-blind trials of treatment for epilepsy in the elderly. The seizures often escape clinical attention, because premonitory symptoms (aura) and secondary generalization into tonic-clonic seizures are both rarer in older patients. On the other hand, sudden loss of consciousness from various causes becomes more common with increasing age, presenting a challenge in differential diagnosis. Treatment is often more complex because of comorbidities and multiple other drugs, and requires a cautious approach. Drug interactions, in particular, require special attention. On the positive side, epileptic seizures in the elderly seem to be more easily controlled by medications than they are in young adults.

Conclusions: Epilepsy is often more difficult to recognize in old age. The treatment is hampered by side effects and drug interactions. Thus, certainty about the diagnosis is indispensable, and the treatment often requires the use of newer-generation antiepileptic drugs.

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Key words: epilepsy, geriatrics, neurological diagnosis, diagnostic testing, misdiagnosis

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Epilepsy was long thought to be a disease of infancy, childhood, adolescence, and young adulthood. Nonetheless, epidemiological studies have revealed that epilepsy is most common among persons aged 75 and older (1, 2) *(figure 1)*. Epilepsy is thus a disease of old age; in fact, it is the third most common type of brain disease in old age, after stroke and the dementing diseases. Not only the public at large, but also members of the health professions, have an inadequate appreciation of epilepsy in the elderly (e1). The purpose of this review, therefore, is to illuminate some of the major principles of the diagnosis and treatment of epilepsy in the elderly, in contrast to epilepsy in younger patients.

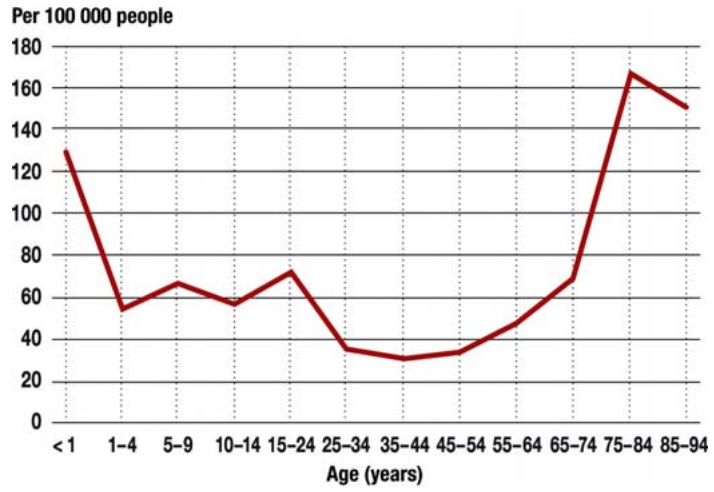
Methods

For this article, the author selectively searched the literature database of the National Library of Medicine, Bethesda, USA ("PubMed") for English or German articles that appeared from 1949 to September 2008 with the words "elderly" and "epilepsy" in the title (epilepsy [ti] AND elderly [ti] AND English or German [la]). These criteria yielded 102 articles, of which 43 were reviews and 9 were case reports. Another search strategy (epilepsy [mh] AND geriatrics [mh] AND English or German [la]) yielded only 74 articles. Relevant chapters in current textbooks were also considered (e2, e3). For this review article, the author considered only original reports containing data from large case series.

Features and seizure types

Epilepsy in the elderly is almost always focal, i.e., symptomatic, although generalized epilepsy can also rarely arise in old age (e4). Epileptic seizures are often not recognized in elderly patients and are instead misdiagnosed as mental changes of uncertain origin, confusion, syncope, memory disorders, or vertigo (3). An episode of altered consciousness and fixed gaze followed by a few minutes of confusion may be the sole clinical manifestation of an epileptic seizure in an elderly patient. Premonitory sensations (aura) are present in about 50% of young adults with focal epilepsy (4), but are rare in older patients (e5). The lack of an aura makes epileptic seizures more difficult to recognize and to classify. Generalized tonic-clonic seizures are recognized by most observers as epileptic and often lead to a diagnosis of epilepsy, yet they are rarer in elderly patients (26%) than in younger ones (65%) (5). The rarity of transition to a generalized tonic-clonic seizure, the common lack of motor phenomena such as automatisms, and the absence of auras are all reasons why epileptic seizures in the elderly often remain undiagnosed. In addition,

FIGURE 1

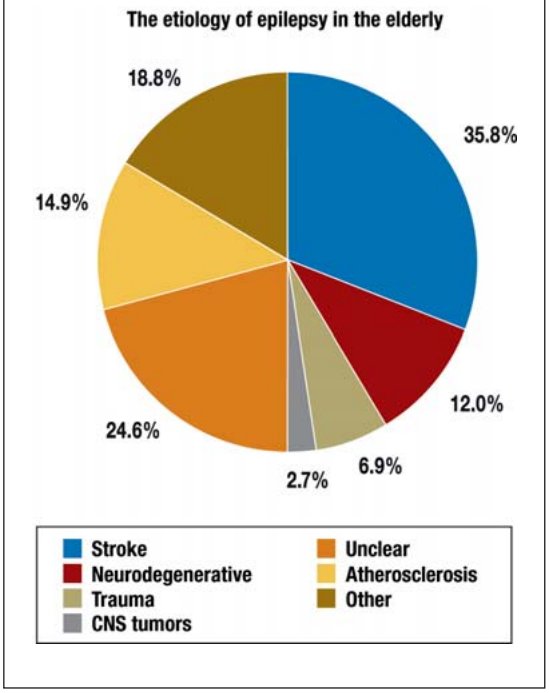


The incidence of new-onset epileptic seizures as a function of age (based on reference [2]).

postictal confusion in an elderly patient can last considerably longer than is usual in younger patients (for hours or days) (6), leading to the erroneous diagnosis of dementia or stroke. Thus, whenever an elderly patient presents with acute confusion, computerized tomography reveals no structural change in the brain, and no other apparent explanation for a cognitive deficit is present (e.g., dehydration, infection, or hyperglycemia), an epileptic seizure or nonconvulsive status epilepticus (12) should be considered and electroencephalography (EEG) should be performed.

The etiology of epilepsy in the elderly (based on reference [1]).

FIGURE 2



Etiology

Any disease of the central nervous system can cause epileptic seizures. Epilepsy in old age is an expression of an underlying disease of the brain. The etiology is an important determinant of the prognosis. Symptomatic epilepsy in younger adults is usually the result of trauma during delivery, congenital malformations or developmental anomalies of the brain, encephalitis, head injury, or a brain tumor. In the elderly, it is usually the expression or the result of a cerebrovascular or neurodegenerative disease *(figure 2)*. Brain tumors play a less important role in old age. In one-third of all elderly patients, the etiology remains unclear (7). Epidemiological studies on patients over age 60 without any history of stroke, trauma, or dementia have shown that the risk of epilepsy in this group is 1.1%. This figure is still twice as high as the corresponding figure for young adults, yet much lower than the incidence of epilepsy when stroke, trauma, or dementia are present (8).

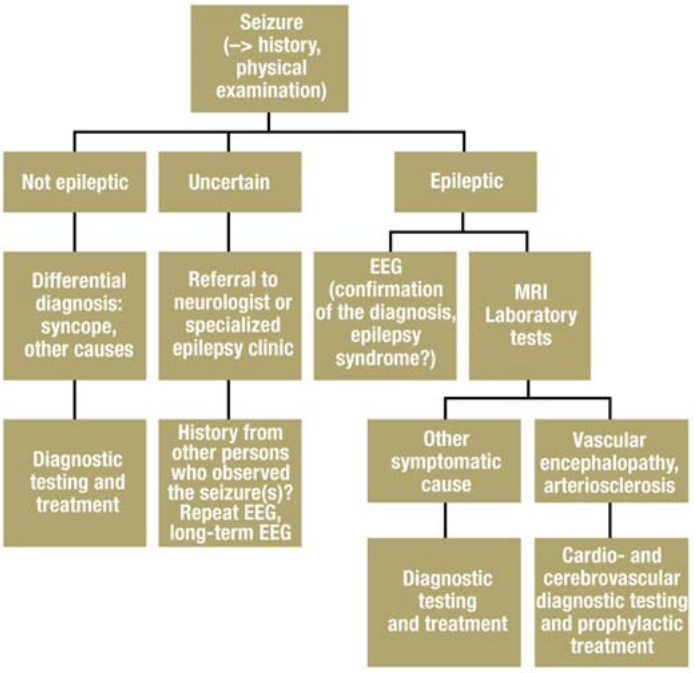
Cerebrovascular diseases are the main cause of epilepsy in old age. Population-based epidemiological studies have shown that stroke multiplies the risk of an epileptic seizure by a factor of 23, and the risk of epilepsy in the first year after the stroke by a factor of 17, compared to the risk in the comparable general population (e6). A distinction can be drawn here between so-called early seizures, which occur as an acute epileptic reaction from the initial hours up to two weeks after the stroke (e7), and late seizures. Data from animal experiments indicate that early seizures after a stroke are due to an acute biochemical abnormality, e.g., exposure to the excitatory neurotransmitter glutamate (e8). Early seizures arise in 2% to 8% of patients, usually in the first 24 to 48 hours after the stroke (9). Isolated epileptic seizures occur in the aftermath of stroke in 3% to 6% of patients (9). Late seizures, on the other hand, occur two weeks or more after the stroke and are due to chronic processes such as the removal of inhibitory influences, scarring, and the formation of new synaptic connections (e9). About half of these patients develop focal epilepsy with recurrent seizures, usually in the first three years after the stroke. The frequency of focal epilepsy after stroke is 2% to 4% and is thus two to four times higher than the incidence in the same age group without stroke (9). Patients with late seizures who also had early seizures have a very high risk of developing focal epilepsy (e7). Further predictors of epilepsy after a stroke are the type of stroke (hemorrhagic > cardioembolic > ischemic due to arteriosclerosis), its localization (cortical > subcortical), and the severity of the stroke as judged by its clinical features and its extent on computerized tomography.

Epileptic seizures in old age can also be the first sign of cerebrovascular disease. In a study of 4709 persons over age 60 without any history of known prior cerebrovascular disease, trauma, dementia, or alcoholism, patients

with epileptic seizures had a five-year risk of stroke that was 2.89 times higher (95% confidence interval: 2.45 to 3.41 times higher) than persons in a control group without seizures (10). Thus, patients who have their first seizure after age 60 should be evaluated for vascular risk factors *(figure 3)*. Cerebrovascular disease is the cause of seizures in every second patient over age 60 presenting with a first seizure; thus, the patient's vascular risk profile should be analyzed, and the patient should be considered at risk for a stroke unless cerebrovascular disease can be ruled out (3).

The incidence of epileptic seizures in patients with Alzheimer's disease increases as the disease progresses; the cumulative incidence over seven years is 8% (11). The incidence per person-year is markedly higher in young patients with Alzheimer's disease (age 50 to 59: 4.3%) than in patients who develop the disease in old age (over age 80: 0.55%). Aside from the age of onset of dementia, further risk factors for epilepsy are the severity of the disease and the presence of epilepsy-typical potentials in the EEG (11). Nonetheless, epileptic seizures are not among the more prominent symptoms of the dementing diseases and are not a major therapeutic problem in this group of patients. It is simply important that they should be recognized when present. Focal epilepsy should be thought of whenever an elderly person presents with transient confusion of uncertain cause. A detailed history should be obtained from another person who observed the episode, and an EEG should be obtained (12).

FIGURE 3



Diagnostic algorithm (author's recommendation, based on limited scientific evidence, in the absence of guidelines)

Treatment

The pharmacotherapy of elderly patients with antiepileptic drugs is complex, requiring special attention to age-related changes in pharmacokinetics and pharmacodynamics (13). No guidelines, systematic reviews, or meta-analyses on this subject are available. There have been only three randomized, controlled, double-blind therapeutic trials of evidence class I or II regarding epilepsy in the elderly (14–16), as well as a number of smaller studies of classes IIa and III (17–22) *(table 1)*. Thus, many clinical decisions about antiepileptic treatment in old age are based on extrapolations of experience and data obtained from younger patients, combined with the general principles of pharmacotherapy in old age (e10). The available studies have shown that lamotrigine and gabapentin are superior to carbamazepine in this age group (14, 15), but the difference disappears when the

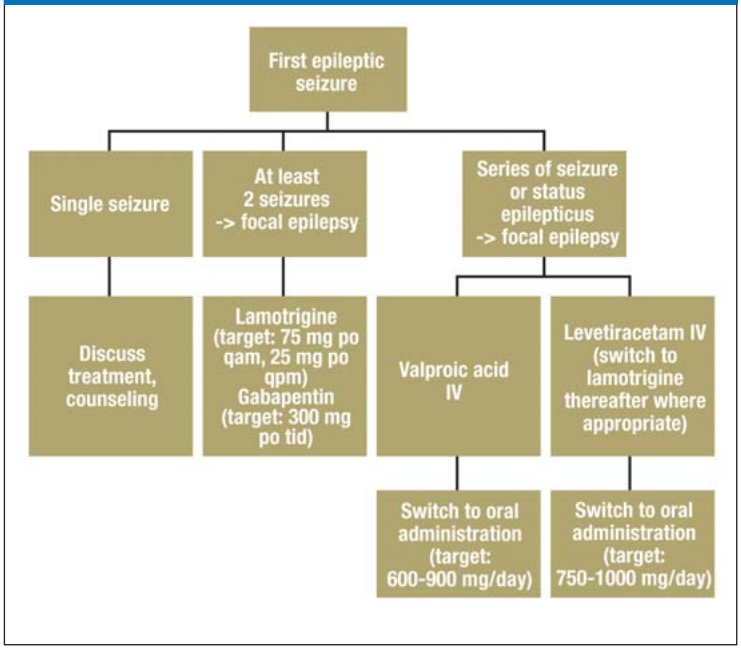
TABLE 1

Overview of therapeutic trials (evidence classes I–III) concerning epilepsy in the elderly

Reference	Year	Type	n	AEDs	Duration (months)	Retention (%)	Target dose (mg)
Evidence class I–II							
Brodie	1999	RC	150	LTG vs. CBZ	6	LTG 71*[1] > CBZ 42	LTG 100, CBZ 400
Rowan	2005	RC	593	GBP vs. LTG vs. CBZ	12	LTG 66*[1] > GBP 49*[1] > CBZ 36	LTG 150, GBP 1500, CBZ 600
Saetre	2007	RC	185	LTG vs. CBZ ret.	12	LTG 73 = CBZ ret. 67	LTG 100, CBZ ret. 400
Evidence class III							
Nieto-B.	2001	RC	49	LTG vs. CBZ	6	LTG 20, CBZ 50	Unclear
Groselj	2005	Retrospective	43	TOP	7	79	TOP 100
Stefan	2008	Open, prospective	107	TOP	9	61	TOP 100

*[1]Percentage of patients still taking the medication at the end of the study; reflects both efficacy and tolerability.
AEDs, antiepileptic drugs, CBZ, carbamazepine; GBP, gabapentin; LTG, lamotrigine; TOP, topiramate.
RC, randomized and controlled; CBZ ret., timed-release carbamazepine.

FIGURE 4



Therapeutic algorithm (author's recommendation, based on limited scientific evidence, in the absence of guidelines)

dose of timed-release carbamazepine is slowly increased up to a lower target dose of 400 mg per day (16). The tested substances did not differ in effectiveness; the difference was rather that lamotrigine and gabapentin were better tolerated.

The treatment of epilepsy seems to be successful in the elderly more often than in young adults (e11): in the best-known therapeutic trial concerning epilepsy in the elderly (23), which involved 622 patients, 62% of the patients over age 65 were free of seizures two years after the start of treatment, as compared to only about 30% of patients aged 40 or younger. A precondition for successful treatment, however, is that the antiepileptic drug is well tolerated and does not interact with other, concurrently taken medications. In the study of Mattson et al. (23), about 64% of patients over age 65 had to stop taking an antiepileptic drug because of side effects, as compared to only about 33% of younger adults. Thus, the treatment of epilepsy in an elderly patient generally requires a search for the medication that is best tolerated and least metabolized (13, e12) *(figure 4)*.

Problems can arise because of increased sensitivity to medications, narrowing of the therapeutic window, and an increased likelihood of drug interactions. The main pharmacokinetic parameters and interactions of antiepileptic drugs are presented in *tables 2–4*. It is evident that the so-called enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, phenobarbital, primidone) generally cannot be recommended for use in elderly patients because of their multifarious interactions (e12, 24).

Age-related changes in pharmacokinetics play a role as early as the drug absorption stage, because gastric secretion, blood volume, blood flow, and gastrointestinal motility are all lower in old age. The serum concentration of medications is heavily influenced by protein binding, mainly to serum albumin, whose concentration is markedly reduced in old age (e13), so that the free fraction of medication in the serum is higher. This influences not only the desired medication effects, but also the undesired ones, and is particularly important in the case of highly protein-bound antiepileptic drugs such as valproic acid, phenytoin, or carbamazepine (e10). The main age-related physiological changes are

- reduced hepatic mass and blood flow, resulting in reduced hepatic metabolism, and
- progressive reduction of renal function.

The ability of the liver to metabolize medication is a function of its enzymatic capacity. The cytochrome P450 enzyme complex, one of the main pathways for the degradation of medications, loses about 10% of its functional capacity every 10 years from age 40 onward; thus, by age 70, its capacity is about 30% lower (e14). Furthermore, there is no clinical parameter of hepatic metabolism with which the patient's hepatic function can be precisely monitored. Hepatic enzymes such as GGT, GOT, and GPT and the serum albumin concentration are not a measure of the liver's ability to metabolize medications (e15). Likewize, the kidneys become smaller and their functional capacity is reduced as patients become older (16). Renal function, unlike hepatic function, can be measured biochemically. Drugs that are eliminated by the kidneys are, therefore, advantageous in elderly patients, because their dose can be adjusted to the patient's renal function.

Dosing: "Start low, aim low"

Elderly patients are more sensitive to the central and systemic side effects of antiepileptic drugs *(table 5)*, particularly their cognitive side effects (e17), partly because of the pharmacokinetic changes mentioned above. This was shown, for example, in double-blinded comparative studies of carbamazepine versus lamotrigine and gabapentin in patients over age 65 (14, 16). All three medications were comparably effective. The retention rate, i.e., the percentage of patients that were still taking the medication one year after starting treatment, was used as a combined measure of drug effectiveness and tolerability and was found to be significantly lower for gabapentin (49%) than for either timed-release carbamazepine (67% for a target dose of 400 mg/day) or lamotrigine (73% for a target dose of 100 mg/day; no significant difference between carbamazepine and lamotrigine) (14, 16). When the target dose of timed-release carbamazepine was set higher (600 mg/day), it was markedly less well tolerated, and only 35.5% of patients remained in the study for a year (14). No controlled studies are available to date for other antiepileptic drugs. Valproic acid should be considered as a valid alternative to carbamazepine for elderly patients (e18); this substance has been in use for many years, can be given in many different forms, and is effective against focal epilepsy. The risk of parkinsonism with cognitive

TABLE 2

The pharmacokinetics, elimination, and interactions of antiepileptic drugs

Drug	Abbreviation	Half-life (hours)	Protein binding (%)	Main route of elimination	Enzyme system involved	Interactions with other AEDs	Remarks
Carbamazepine	CBZ	5–26	75	Hepatic: oxidation to epoxide (65%) and glucuronidation (15%)	CYP3A4	VPA, LTG, TPM, ZNS, LEV (25%) and benzodiazepines reduced	Epoxide metabolite is active and commonly causes side effects
Phenobarbital	PB	77–128	55	Hepatic: oxidation and glucuronidation	CYP2C9	CBZ, VPA, LTG, TPM, ZNS, LEV (25%) and benzodiazepines reduced	
Phenytoin	DPH	7–42	90	Hepatic: oxidation	CYP2C9	CBZ, VPA, LTG, TPM, ZNS, LEV (25%) and benzodiazepines reduced	
Valproic acid	VPA	9–15	90	Hepatic: glucuronidation (50%) and oxidation	UGT2B7	LTG markedly, CBZ-epoxide and PB mildly increased; CBZ mildly reduced	Oxidation by mitochondrial oxidases and CYPs
Newer antiepileptic drugs							
Gabapentin	GBP	5–7	< 3	Renal			
Lacosamide	LCM	13	< 15	Renal (95%)		None known	
Lamotrigine	LTG	30	55	Hepatic: glucuronidation (>65%)	UGT1A4	25% reduction VPA	
Levetiracetam	LEV	6–8	< 10	Renal (75%), hepatic hydrolysis	Hydrolase	–	Hydrolysis 25%
Oxcarbazepine (active metabolite MHD)	OXC	9 (MHD)	40 (MHD)	Hepatic: glucuronidation (MHD)	Aldoketo reductase	DPH 40% increased	
Pregabaline	PGB	6	<1	Renal (> 90%)		–	
Topiramate	TPM	18–23	15	Renal, oxidation (15%)	CYPs (to a slight extend)	DPH 25% increased	
Zonisamide	ZNS	63	40	Renal, oxidation, reduction	CYP3A4	None known	

Modified from Levy et al. in Engel and Pedley (eds.): Epilepsy: A Comprehensive Textbook. Lippincott Williams & Wilkins, 2008. MHD, monohydroxy-derivative; AED, antiepileptic drug

TABLE 3

Drugs that elevate the serum concentration of antiepileptic drugs, usually by enzyme inhibition

Affected substance		Interfering substance
Carbamazepine	Antidepressants	Fluoxetine, fluvoxamine, nefazodone, sertraline, trazodone, viloxazine
	Antimicrobial agents	Erythromycin, clarithromycin, fluconazole, isoniazide, ketoconazole, metronidazole, ritonavir, troleadomycin
	Miscellaneous	Cimetidine, diltiazem, quetiapine, risperidone, ticlopidine, verapamil
Lamotrigine	Antidepressants	Sertraline
Phenobarbital	Antimicrobial agents	Chloramphenicol
	Miscellaneous	Dextropropoxyphene
Phenytoin	Antidepressants	Fluoxetine, fluvoxamine, imipramine, sertraline, trazodone, viloxazine
	Antimicrobial agents	Chloramphenicol, fluconazole, isoniazide, miconazole, sulfaphenazole
	Antineoplastic agents	Doxyfluridine, fluorouracil, tamoxifen, tegafur, UFT
	Miscellaneous	Allopurinol, amiodarone, azapropazone, cimetidine, chlorpheniramine, dextropropoxyphene, diltiazem, disulfiram, omeprazole, phenylbutazone, sulfinpyrazone, tacrolimus, ticlopidine, tolbutamide
Valproic acid	Antidepressants	Sertraline
	Antimicrobial agents	Isoniazide
	Miscellaneous	Cimetidine

Only effects described in the literature are included in the table; after Perucca E, Br J Clin Pharmacol, 2005

TABLE 4

Medications whose serum concentrations are lowered by enzyme-inducing antiepileptic drugs (CBZ, PB, DPH, and PRM*[1])

Antidepressants	Amitriptyline, bupropion, citalopram, clomipramine, desipramine, desmethylclomipramine, doxepine, imipramine, mianserin, mirtazapine, nefazodone, nortriptyline, poroxetine, protriptyline
Antimicrobial agents	Albendazole, doxycycline, griseofulvin, indinavir, itraconazole, metronidazole, praziquantel
Antineoplastic agents	9-aminocampthotecin, busulfan, cyclophosphamide, etoposide, iosfamide, irinotecan, methotrexate, nitroureas, paclitaxel, procarbazine, temoxifen, teniposide, thiotepa, vinca alkaloids
Antipsychotic agents	Chlorpromazine, clozapine, haloperidol, mesoridazine, olanzapine, quetiapine, risperidone, ziprasidone
Benzodiazepines	Alprazolam, clobazam, clonazepam, desmethyldiazepam, diazepam, midazolam
Cardiovascular medications	Alprenolol, amiodarone, atorvastatin, dicoumarol, digoxin, disopyramide, felodipine, metoprolol, mexiletine, nifedipine, nimodipine, nisoldipine, propranolol, quinidine, simvastatin, verapamil (oral), phenprocoumone
Immune suppressants	Cyclosporine A, sirolimus, tacrolimus
Steroids	Cortisol, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, oral contraceptives (also with oxcarbazepine, topiramate >200 mg/day)
Miscellaneous	Fentanyl, methadone, metyrapone, misonidazole, paracetamol, pethidine, theophylline, thyroxine, vecuronium

*[1]CBZ, carbamazepine; PB, phenobarbital; DPH, phenytoin; PRM, primidone;
Only effects described in the literature are included in the table; after Perucca E, Br J Clin Pharmacol, 2005

TABLE 5

The frequency (in %, rounded) of the main adverse effects of antiepileptic drugs*[1]

Category	Type	CBZ*[1]	GBP*[2]*[7]	LTG*[2]*[7]	LEV*[3]	OXC*[4]	TOP*[5]*[7]	VPA*[6]
Neurotoxic	Diplopia	8	8	7	–	15	–	16
	Affective disturbance	33	27	30	6	–	10	6
	Gait disturbance/ataxia	25	29	28	–	–	10	–
	Cognitive	29	30	23	–		3–5	6
	Headache	18	15	19	14		13	31
	Fatigue	51	46	40	17	19	13	27
	Nystagmus	14	14	14	–	20		8
	Dizziness	32	28	27	11	30	13	25
	Tremor	17	22	25	–	8		25
	Paresthesiae			–	–	–	13	–
Systemic	Gastrointestinal	32	24	34	–	–	–	48
	Weight loss	–	–	–	–	–	5	
	Weight gain	– (> 8kg)	11 (> 8kg)	– (> 8kg)	–	13	–	12–16
	Hair loss	–	–	–	–	–	–	14
	Impotence	8	9	–	–	–	–	–
	Edema	9	20	10	–	–	–	–
	Hyponatremia	11	–	7	–	22	–	–
Idiosyncratic	Rash	10	5	–	–	3	–	–
	Infection	–	–	–	13	–	–	–

CBZ, carbamazepine; GBP, gabapentin; LTG, lamotrigine; LEV, Levetiracetam; OXC, oxcarbazepine; TOP, topiramate; VPA, valproic acid.
*[1] Side effects occurring with greater than 5% frequency in AEDs licensed for use as monotherapy;
*[2] Rowan et al., Neurology, 2005;
*[3] V. Biton in Levy, Mattson, Meldrum, and Perucca: Antiepileptic Drugs, 5th ed.;
*[4] G. Krämer in Levy, Mattson, Meldrum, and Perucca: Antiepileptic Drugs, 5th ed.;
*[5] Ramsay et al., Epilepsia, 2008;
*[6] Genton and Gelisse in Levy, Mattson, Meldrum, and Perucca: Antiepileptic Drugs, 5th ed.;
*[7] based on data in elderly patients

Key messages

- Epileptic seizures are more common among persons over 70 than in any other age group.
- The clinical manifestations of epileptic seizures in the elderly are different from those of younger patients: auras and generalized tonic-clonic seizures are rarer, while status epilepticus is more common.
- Epileptic seizures in the elderly are often not diagnosed; for improved differential diagnosis, long-term EEG and ECG recordings should be performed more often.
- A first epileptic seizure in a patient over 60 years old is more likely to be due to cerebrovascular disease than to any other etiology.
- When elderly patients are treated with antiepileptic drugs, the standard target dose should be half that used in younger adults, and drug loading should be performed half as rapidly, so that adverse effects can be avoided.

decline when valproic acid is used is estimated at 2% (e19) and seems to be higher in old age, yet the lack of tiredness and motor slowing and the absence of hepatic enzyme induction are advantages over carbamazepine in this age group. Levetiracetam also deserves mention because of its favorable side-effect profile and pharmacokinetics (21); it is recommended by epileptologists (25). No results of controlled trials in the elderly are yet available for either valproic acid or levetiracetam. In a study involving 73 elderly patients, both side effects and good seizure control were associated, in most patients, with serum concentrations of carbamazepine or valproic acid that were at, or well below, the lower limit of the so-called therapeutic range (e20). Thus, it can generally be recommended that, when an antiepileptic drug is initially given to an elderly patient (>70 years of age), the target dose should be about half that of young adults, and the rate of increase of the dose should also be half as high, whenever possible (e21).

Overview

Focal epilepsy is more common among the elderly than in any other age group. The current state of knowledge in this field, and the clinical trials that have been performed to date, still do not answer many important questions for clinical practice, because only a few trials have included elderly patients. As epilepsy in the elderly has less obvious clinical manifestations and is often overlooked, a reliable history from a person who observed the episode(s) and/or adequate data from an EEG or video-EEG recording are important means of assuring that the diagnosis will not be missed. In the coming years, a major effort should be made to improve our understanding of the clinical course and optimal treatment of epilepsy in this rapidly growing segment of the population: by the year 2020, it is estimated that every second person in Germany will be over age 50, and some 7% of the population will be 80 or older.

Conflict of interest statement
The author has received lecture honoraria from UCB, Pfizer, and Sanofi-Aventis, as well as study support (Step One) from UCB. He has also received author's fees from Sanofi-Aventis and UCB and serves on advisory boards for Pfizer and UCB.

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REVIEW ARTICLE

Epilepsy in the Elderly

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