PRACTICAL DRUG SAFETY

Drug Safety 2001; 24 (13): 991-1015
0114-5916/01/0013-0991/$22.00/0

Treating Epilepsy in the Elderly
Safety Considerations

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Abstract

The incidence of epilepsy increases with advancing age. Epilepsy in the elderly has different aetiologies from that in younger populations, cerebrovascular disease being the most common condition associated with seizures. Partial seizures are the predominant seizure type in older patients. A diagnosis of epilepsy in the elderly is based mainly on the history and is frequently delayed. In addition, seizure imitators are especially frequent. In many cases ancillary tests for diagnosis may show normal age-related variants, sometimes making results difficult to interpret. Treating epilepsy in the elderly is problematic due to a number of issues that relate to age and comorbidity. The physical changes associated with increasing age frequently lead to changes in the pharmacokinetics of many anticonvulsants. The treatment of epilepsy in the elderly is also complicated by the existence of other diseases that might affect the metabolism or excretion of anticonvulsants and the presence of concomitant medications that might interact with them. Moreover, specific trials of anticonvulsants in the aged population are scarce. General guidelines for treatment include starting at lower doses, slowing the titration schedule, individualising the choice of anticonvulsant to the characteristics of the patient, avoiding anticonvulsants with important cognitive or sedative adverse effects, and where possible, treating with monotherapy.

The world population, especially in industrialised countries, is aging, and this is leading to the more frequent manifestation of brain disorders. Epilepsy in the elderly is increasingly common and becoming an important medical problem. Diagnosing and treating epilepsy in the aged population is associated with different challenges from those in childhood or adult epilepsy. Epilepsy in the elderly has different aetiologies and frequent comorbidity, and concomitant medications are common. In addition, the elderly handle anticonvulsants somewhat differently in a pharmacokinetic sense and they are more susceptible to experiencing adverse events.

1. Incidence and Prevalence of Epilepsy

Seizures and epilepsy are frequent in the elderly. Acute symptomatic seizures are those occurring at the time of an acute brain insult and are not synonymous with epilepsy. Epilepsy is defined as recurrent unprovoked seizures. This differentiation is important when considering prognosis and deciding on long-term treatment.

In the elderly, acute symptomatic seizures are frequent. The annual incidence in patients over the age of 60 years reaches 90 per 100 000 persons, much higher than in adult populations (16 per 100 000 persons per year).[1,2] Elderly men are more prone to acute symptomatic seizures than elderly women (130 per 100 000 men *vs* 60 per 100 000 women), possibly because of the higher incidence of cerebrovascular insults or alcohol abuse.[1]

A large study has analysed the incidence of epilepsy and unprovoked seizures and has shown two peaks of incidence, one in the first year of life and another, higher, one in persons aged >74 years.[3] The annual incidence of unprovoked seizures in those aged >60 years is 150 per 100 000 persons. The cumulative incidence of epilepsy through age 74 years was 3.1%. Other studies have shown similar high incidence in the aged population.[4-6]

The prevalence of epilepsy in elderly patients

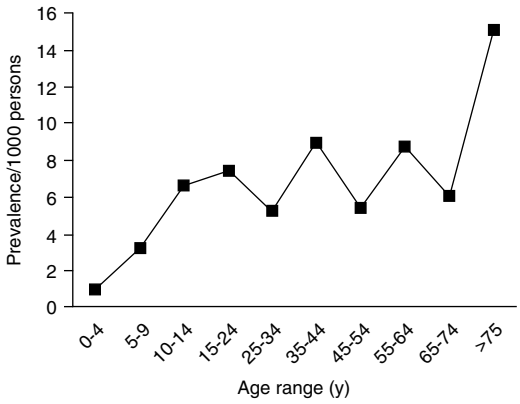

Fig. 1. Prevalence of epilepsy in Rochester, Minnesota, USA (reproduced from Hauser et al.,[7] with permission).

ranges from 6.01 per 1000 persons (65 to 69 years) to 7.73 per 1000 persons (≥85 years).[4] In another study, conducted in Rochester, Minnesota, US, a similarly high prevalence was seen between 65 and 74 years of age (6 per 1000 persons), but much higher in the population >75 years (15 per 1000 persons)[7] [figure 1]. Lower prevalence data were shown in the Rotterdam study in patients aged 55 to 95 years. The overall prevalence of active epilepsy in this study was 0.9%. The prevalence increased with age from 0.7% for those aged 55 to 64 years to 1.2% for those aged 85 to 94 years. The increase with age was detected among both men and women.[8]

2. Type of Seizures and Epilepsy

Elderly persons have a higher incidence of partial onset seizures than children. In most studies, half to two-thirds of the seizures are accounted as focal (figure 2).[5,9,10] However, it is highly probable that what are termed generalised (convulsive) seizures are in fact secondarily generalised. Generalised (idiopathic) epilepsies *per se* do not appear for the first time in the elderly, and most, if not all, unprovoked convulsive or nonconvulsive seizures are partial or secondarily generalised. Only exceptional cases have been reported of juvenile myoclonic epilepsy appearing over the age of 40 years[11,12] and of generalised epilepsy with spike-wave complexes.[13,14]

3. Aetiology

The proportion of unprovoked seizures with an identified presumptive cause increases with advancing age. In population-based studies of epilepsy at all ages, a definite aetiology is identified only in one-third of patients (fig. 3). However, in the elderly a presumed aetiology can be identified in 70% of cases.[3] Compared with children or adults, elderly persons with epilepsy have a different gamut of aetiologies related to the prevalent diseases at this age. Stroke is the most common cause, detected in 45% of patients at ages >60 years. Other causes detected are tumours (11%) or Alzheimer's disease (7%).[3,5]

3.1 Cerebrovascular Disease

Compared with the general population, patients with cerebrovascular disease have an increased risk of developing epilepsy.[15] Poststroke seizures can be divided into two types: early onset (first 7 to 14 days) and late onset seizures. This distinction

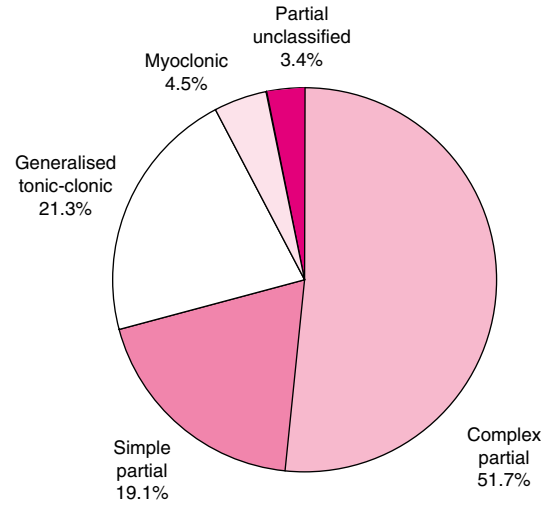

Fig. 2. Incidence of different types of seizures in patients older than 60 years (reproduced from Hauser et al.,[3] with permission).

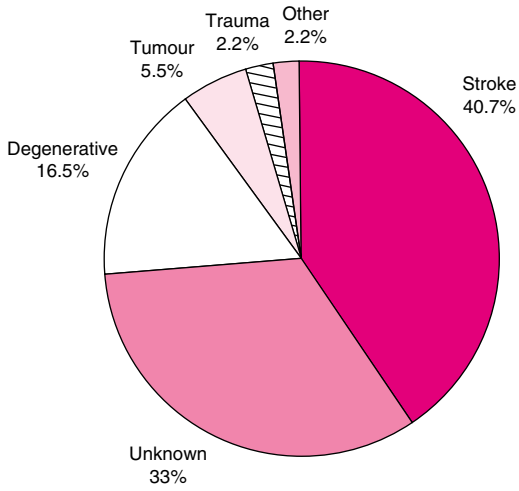

Fig. 3. Aetiology of epilepsy in patients older than 60 years (reproduced from Hauser et al.,[3] with permission).

is important because significantly fewer patients with early onset seizures develop another seizure, i.e. epilepsy, than patients with late onset seizures.[16] During the acute period poststroke the incidence of acute symptomatic seizures reaches 6%.[17,18] On the other hand, the cumulative incidence of late onset epilepsy in poststroke patients reaches 19% at 6 years.[19] Factors affecting the risk of recurrence are early seizure occurrence, the severity of the stroke (extension of the infarct), and the presence of haemorrhage.[19-21] Also, patients with a late onset seizure have a higher likelihood of recurrence.[16] Interestingly, it has been shown that the prevalence of previous epilepsy in patients with a first vascular event is 4.5%, much higher than the 0.6% in the control population, suggesting that risk factors for vascular disease could, in themselves, be associated with higher rates of epilepsy.[22] In fact, risk factors for cerebrovascular disease (hypertension, hypercholesterolaemia) are also independent risk factors for epilepsy in the elderly population.[15,23]

3.2 Dementia

Alzheimer's disease and other dementias are associated with a 5- to 10-fold increase in risk of epilepsy when compared with that in a control population.[24,25] 15% of patients diagnosed with Alzheimer's disease will develop epilepsy by the tenth year after diagnosis.[24]

3.3 Tumours

Although the incidence of brain tumours increases with age, this is a relatively infrequent cause of epilepsy in the elderly.[3] Elderly persons with brain tumours present more often with confusion, aphasia or memory loss than with seizures.[26]

3.4 Metabolic Complications

Different intercurrent diseases can provoke acute symptomatic seizures. Alterations of electrolytes, alcohol abuse or deprivation, and hyperglycaemia are frequent seizure triggers.[27-29]

3.5 Drug-Induced Seizures

Elderly persons have a special susceptibility to drug-induced seizures, which can be associated with age-related pharmacokinetic changes, concomitant treatment with multiple drugs, and the build-up of multiple risk factors for seizures or epilepsy (previous structural disease or epilepsy, hypertension).

4. Diagnosis

Diagnosis of seizures or epilepsy is based on clinical history, trying to find out the type of seizure (generalised versus partial) and the predisposing factors for or aetiology of the seizures. Correct diagnosis is frequently delayed in the elderly, mainly because of lack of awareness of partial seizures by the public and healthcare providers and the concept of trying to attribute all of the patients' symptoms to a single diagnosis.[30] Ancillary tests can be useful for confirming the diagnosis.

4.1 Electroencephalogram

Electroencephalogram (EEG) interpretation in the elderly has two distinct differences from that in younger persons: first, there are frequent normal variant patterns that could be erroneously interpreted as abnormal or epileptogenic;[31] second, re-

cording of drowsiness or sleep is more frequent, thus increasing the complexity of the interpretation.[32] Interictal epileptiform activity is present on the first EEG in 26% of patients with seizure onset after 60 years, which is substantially lower than that reported in populations with epilepsy as a whole. Most epileptogenic activity is focal and there are no major differences in likelihood of spike detection depending on the underlying cause of the seizures.[33] Occasionally, video-EEG can be useful for diagnosis of seizures.[34] EEG can help in taking a therapeutic decision. For example, van Donselaar et al.[35] showed that the presence of epileptiform activity in the EEG provides a cumulative risk of seizure recurrence at 2 years of 80%, while patients with normal EEG have a recurrence risk of 12%.

4.2 Brain Imaging

Computed tomography or magnetic resonance imaging (MRI) are indicated in all aged individuals with new-onset seizures. Both techniques are useful for detecting structural lesions, but MRI is the method of choice because of its better resolution. In the elderly, MRI can easily show lacunae, small tumours, leucoaraiosis or hippocampal sclerosis, which are not well detected by computed tomography.[36] In persons aged >60 years, hyperintense T2-weighted lesions in the white matter are frequent and their significance remains uncertain.[37]

5. Status Epilepticus

The incidence of status epilepticus peaks in infancy and in the elderly[38,39] (fig. 4). In persons aged >60 years the incidence of status epilepticus reaches 18.3 per 100 000 persons, much higher than in adults (up to 10.9 per 100 000 persons). The cumulative incidence of status epilepticus is 4 per 1000 persons to age 75 years and shows the greatest increase after age 60 years. In the elderly, status epilepticus tends to be of longer duration.[38] Acute symptomatic aetiology is most frequent, especially related to a stroke. Status epilepticus has a high mortality, reaching 35% in the elderly. Two-thirds of the patients with status epilepticus have the convulsive form and the remainder have the non-convulsive form.[38]

Status epilepticus is common among patients with poststroke seizures, occurring in nearly one-fifth of them. In most patients the status is the first seizure ever.[40] In the setting of acute stroke, status epilepticus has a very high mortality. This is related not only to the severity of the underlying aetiology, but also to the synergistic effect of combined injuries from status and cerebral vascular ischaemia.[41] Curiously enough, status epilepticus as the presenting sign does not necessarily predict subsequent epilepsy.[40]

6. Differential Diagnosis

In the elderly population seizure imitators are especially frequent and may coexist with true seizures. In most cases, taking a detailed history from the patient and witnesses and a thorough physical examination allows differentiation to be made. Potential causes of transient loss of consciousness are discussed in the following sections.

6.1 Syncope

In the elderly syncope can appear without the typical premonitory signs and symptoms that make its diagnosis easy in younger populations.[42] Cardiogenic syncope, carotid sinus hypersensitivity,

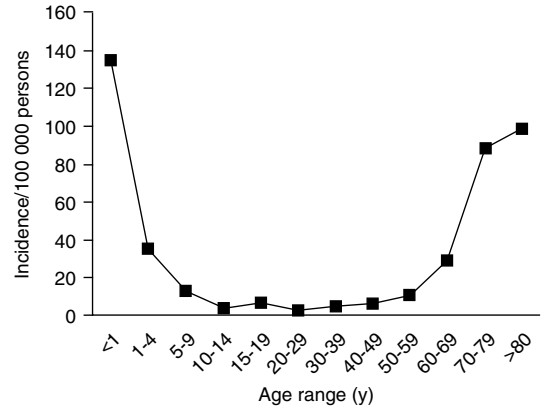

Fig. 4. Prevalence of status epilepticus in Rochester, Minnesota, USA (reproduced from Hesdorffer et al.,[38] with permission).

and syncopes due to orthostatic hypotension are the most frequent types, with vasovagal syncope being rare. An electrocardiogram should be done in all elderly patients who have had a first seizure. Depending on the diagnostic suspicion, other tests would be appropriate.

Transient ischaemic attacks can occasionally appear in association with seizures, usually simple partial motor or secondarily generalised seizures. In these cases hemiparesis due to stroke can be misinterpreted as Todd's paresis.

6.2 Dementia

In certain situations an epileptic pseudodementia may occur. This problem may be present in patients in whom memory dysfunction is due to unrecognised complex partial seizures with subtle clinical signs or loss of awareness, or seizures that occur during sleep.[43]

6.3 Sleep Disorders

Certain sleep disorders that are more frequent in the elderly (REM-behaviour disorder or periodic leg movements) can be confused with epilepsy.[44] Correct interpretation of the symptoms and ancillary tests can be valuable to make a correct diagnosis.

Psychogenic seizures are rare in the elderly. Diagnosis is facilitated by a high level of suspicion and video-EEG recording.[45]

7. Pharmacokinetics of Anticonvulsants in the Elderly

Pharmacokinetic properties of anticonvulsants are different in the elderly in relation to multiple bodily changes associated with age (table I).

Gastrointestinal absorption and bioavailability is usually good and linear for all anticonvulsants, except for gabapentin and, at high doses, valproic acid (sodium valproate). In the elderly, changes in the digestive tract consisting of reduction of the absorption area, perfusion, motility and acid secretion are observed. However, these changes are usually of little significance for absorption of anticonvulsants. Probably the major problem in this area is the concomitant use of antacids that may reduce the absorption of some anticonvulsants.

Table I. Summary of the pharmacokinetic characteristics of the most commonly used anticonvulsants

Drug	Protein (albumin) binding	Half-life	Metabolism	Clearance	Interaction potential	Adverse events[a]	Monotherapy
Carbamazepine	↓	↔ (6-12h)	20% ↓	Hepatic clearance ↓ up to 40%	High	Hyponatraemia, cardiac conduction	Yes
Phenytoin	Slight ↓	↑ to 40-60h	↓	Hepatic clearance ↓	High	Osteopenia	Yes
Valproic acid (sodium valproate)	↓	↑ to 12-22h	↔	Hepatic clearance ↓ for the free fraction	Medium	Tremor, parkinsonism	Yes
Phenobarbital (phenobarbitone)	↔	↑ up to 120h	↓	Hepatic and renal clearance ↓	High	Cognitive effects, osteopenia	Yes
Lamotrigine	↔	↔	↔	Hepatic clearance ↓ up to 40%	Medium		Yes
Gabapentin	↔	↔	↔	Renal clearance often ↓	No		Yes
Tiagabine	↔	↔	↔	Hepatic clearance ↓ up to 40%	Low		Add-on
Topiramate	↔	↔	↔	↔	Low	Cognitive effects, renal calculi	Yes
Oxcarbazepine	↔	↔	↔	Hepatic clearance ↓	Low	Hyponatraemia	Yes
Levetiracetam	↔	↑ to 10-11h	↔	↔	No		Add-on
Zonisamide	↔	↔	↔	Glomerular filtration rate ↓	Low	Renal calculi	Add-on

a Adverse events that may be especially relevant in the elderly.

↑ = increase; ↓ = decrease; ↔ = no change.

Total body water decreases with age, altering the distribution volume and half-life of some drugs. For example, the half-life of diazepam increases from 20 hours in adults to 90 hours in persons aged >80 years.[46] In addition, decrease of musculature and in fat proportion may also lead to changes in the volume of distribution.

In the elderly there is a variable decrease in albumin, leading to a reduction of protein binding by anticonvulsants.[47] This affects highly protein-bound anticonvulsants, but also may have an effect on others that are less highly bound. For example, carbamazepine is not highly protein bound. However, its major ligand in the serum is non-glycated albumin, which decreases with age. This alteration leads to an increase in free carbamazepine concentrations, thus inducing an increase in the sensitivity of the pharmacological effects of carbamazepine and the risk of drug interactions.[48]

With age there is a decrease in liver volume, weight and perfusion.[49] There is also a reduction in protein synthesis potentially affecting drugs that have high protein binding (such as valproic acid). Moreover, metabolic activity is reduced. Phase 1 reactions such as oxidation, reduction or hydrolysis decrease, leading to a reduction of metabolism of certain anticonvulsants (carbamazepine, phenytoin, oxcarbazepine). Phase 2 reactions such as glucuronidation or acetylation are reduced, but in general have no major effect on anticonvulsant metabolism.

Decreases in glomerular filtration rate, creatinine clearance, and tubular secretion and absorption are observed with age.[49]

In addition, pharmacodynamic changes that are difficult to analyse can explain the greater frequency or intensity of CNS-related adverse events in the elderly.[50,51] This could be related to changes in receptor sensitivity (decrease in number, increase in sensitivity) leading to a greater response to and toxicity from anticonvulsants.[51,52]

In view of these pharmacokinetic problems, the ideal anticonvulsant for use in an elderly patient should be well absorbed, not protein bound, not metabolised, with a half-life that could permit once or twice daily administration, cleared by renal elimination, and devoid of any interaction.[53] No such drug exists, but new anticonvulsants are generally closer to this ideal pharmacology.

8. Use of Anticonvulsants in the Elderly

Suggestions for anticonvulsant use in the elderly are summarised in table II.

8.1 Carbamazepine

Carbamazepine is effective in partial and generalised tonic-clonic seizures. Its major mechanism of action is stabilisation of the neural membranes through its action on sodium channels.[54]

Carbamazepine is well absorbed. It is extensively metabolised by the liver with nonlinear kinetics due to autoinduction through cytochrome P450 (CYP) enzymes. Autoinduction is responsible for a decrease in its serum concentration after the first 3 or 4 weeks of treatment.[55] Metabolism of carbamazepine by CYP enzymes leads to a number of interactions. In addition, carbamazepine has a major metabolite, carbamazepine-10,11 epoxide, which is also an anticonvulsant but is responsible for the adverse effects of carbamazepine.[56] Both carbamazepine and carbamazepine epoxide are protein bound (65 to 85%). Changes in albumin and α_1-acid glycoprotein might increase the free fraction.[46] Carbamazepine is 99% cleared by the liver. In the elderly, clearance may be reduced by up to 40%.[57] Elimination half-life is between 6 and 12 hours, but twice daily administration can be used in monotherapy with slow-release preparations.

In comparative trials with classical anticonvulsants, carbamazepine monotherapy has shown similar efficacy to primidone, phenytoin and phenobarbital and similar efficacy to valproic acid for secondarily generalised seizures, but superior efficacy for partial seizures.[58-63] The tolerability of carbamazepine was similar to that of phenytoin or valproic acid, but significantly superior to that of phenobarbital or primidone.[58-63] Direct comparisons with new anticonvulsants have shown that carbamazepine has better efficacy than vigabatrin in adults[64] and similar efficacy to oxcarbazepine in adults[65] and lamotrigine in the elderly,[66] but

Table II. Suggestions for use of anticonvulsants in the elderly

Carbamazepine	Despite its pharmacokinetic drawbacks, carbamazepine remains a first-line anticonvulsant in the elderly
	Start at a low dose (i.e. 100 mg/day)
	Titrate at a slow pace (by increments of 100 mg/wk)
	Measure sodium levels if symptoms arise (lethargy, nausea, confusion)
	Avoid if possible in patients with pre-existing hepatic disease or low protein
Phenytoin	A lower starting dose and lower dose increments are recommended to avoid toxicity (starting dose of 200 mg/day with increments of 30 mg/day)
	Increase the dose if concentrations are subtherapeutic by minimal increments (i.e. 30 mg/day)
	Give vitamin D supplementation and measure bone density periodically
	Avoid in patients with pre-existing hepatic disease or low protein
	Avoid in patients comedicated, especially with digoxin or warfarin
Phenobarbital (phenobarbitone)	Not the drug of choice for initial treatment of epilepsy in the elderly
	Initial dose should be lower than in adults (50 mg/day) with lower dose increments (50 mg/day)
Primidone	Not the drug of choice for initial treatment of epilepsy in the elderly
	Initial dose should be lower than in adults (62.5 mg/day) with increments in 62.5mg steps
Valproic acid (sodium valproate)	A first-line anticonvulsant for the treatment of partial or generalised seizures in the elderly
	Give with food to avoid peak concentrations or use the slow-release preparation
	Titrate more slowly and aim to give lower total doses than in adults (increments of 300mg recommended)
	Avoid concomitant use with phenytoin or phenobarbital
	Avoid in patients with hepatic disease or low protein
Benzodiazepines	Avoid long-term use of benzodiazepines
Lamotrigine	Well tolerated and effective in the elderly; indicated as a first-line anticonvulsant
	Slow titration is necessary, especially in patients treated with valproic acid
Tiagabine	Use as add-on anticonvulsant. At present there is not enough evidence for its use as a monotherapy
	Avoid in patients with pre-existing liver disease
Topiramate	Use as add-on; currently not indicated as first-line monotherapy
	Cognitive adverse events may reduce its use in the elderly
Gabapentin	First-line anticonvulsant for the treatment of partial epilepsy in the elderly
	Use with caution in patients with pre-existing severe renal disease
Oxcarbazepine	Not the drug of choice for initial treatment of epilepsy in the elderly
	Care should be taken when using oxcarbazepine in the elderly because of hyponatraemia and the use of concomitant medication
Zonisamide	May be useful as an add-on medication for elderly patients with partial seizures
	Use with caution in patients with pre-existing renal disease
Levetiracetam	Indicated as add-on therapy for partial seizures
	Use with caution in patients with renal disease
Felbamate	Not indicated in elderly patients unless no other medication is available
Vigabatrin	Use is restricted; should not be used unless no other anticonvulsant is available

poorer tolerability than each of the new anticonvulsants.

The major adverse events associated with carbamazepine are CNS related. Hyponatraemia, known to occur with carbamazepine administration, is more frequent in elderly patients and sodium levels need to be measured if symptoms occur.[67] Carbamazepine can rarely induce sinus node dysfunction or atrioventricular block in the elderly.[68]

8.2 Phenytoin

Phenytoin is effective in treating partial and generalised tonic-clonic seizures. Its major mechanism of action is related to the reduction of entry of sodium and calcium into the cell.[54]

Phenytoin is well absorbed. It is metabolised by the CYP enzyme system and the enzymes become saturated at a low concentration, conferring nonlinear

kinetics. The metabolism of phenytoin is reduced in the elderly and saturation is achieved at a lower concentration.[69] The daily doses required to achieve identical serum concentrations are 21% lower for persons aged >60 years than for adults.[70] Phenytoin has high protein binding (95%), so that free concentrations can be useful to monitor toxicity.[71] Excretion of free phenytoin may be impaired with decreased renal function, with associated increases in free serum concentrations.[72] Average half-life is about 30 hours, and phenytoin can be given once daily. Phenytoin has a high interaction potential because of its microsomal enzyme induction and its high protein binding.

Phenytoin has shown similar efficacy to valproic acid, carbamazepine, primidone and phenobarbital in several monotherapy trials in new onset epilepsy both in partial and generalised seizures.[58-60,63,73] A comparative trial with lamotrigine has shown that both drugs are equally effective against partial and generalised seizures but lamotrigine is better tolerated and has a lower incidence of CNS adverse effects.[74]

Phenytoin may be more deleterious to higher cognitive tasks than carbamazepine or valproic acid.[75] Moreover, phenytoin can be especially detrimental in the elderly by enhancing pre-existing cognitive deficits. Phenytoin reduces bone calcium through changes in vitamin D metabolism and can lead to generalised osteomalacia in aged persons.[76,77]

8.3 Phenobarbital (Phenobarbitone)

Phenobarbital is effective in partial and generalised seizures. It acts on the γ-aminobutyric acid (GABA) receptor, prolonging the opening of the chloride channels and thus enhancing inhibition. Phenobarbital also blocks excitatory responses to glutamate, mainly through α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors.[54]

Phenobarbital is well absorbed and has moderate protein binding (50%) and a very long half-life (80 hours). It is extensively metabolised through the liver and induces microsomal enzymes, providing a high interaction potential. Clearance is 70% hepatic and 30% renal. In the elderly, phenobarbital half-life increases to 120 hours because of reduced liver and renal clearance.[49]

Phenobarbital is as effective as other classic anticonvulsants (carbamazepine, valproic acid, phenytoin, primidone), but is significantly more toxic.[58,59] The most common adverse events associated with phenobarbital are CNS related. Another relevant adverse event in the elderly is osteomalacia.[77]

8.4 Primidone

Primidone is chemically similar to phenobarbital and has similar postulated mechanisms of action.

Primidone has high bioavailability and low protein binding. It is metabolised by the liver, inducing microsomal enzymes, and has two active metabolites [phenobarbital and phenylethylmalonamide (PEMA)], giving a high interaction potential. Clearance is 90% renal unchanged. In the elderly, reduced renal clearance of the PEMA metabolite[78] and of phenobarbital might reduce tolerability.

Primidone has similar efficacy to phenobarbital, carbamazepine or phenytoin but, similarly to phenobarbital, is not as well tolerated.[58,78]

8.5 Valproic Acid (Sodium Valproate)

Valproic acid is a broad spectrum anticonvulsant useful in both localisation-related and generalised epilepsies. Valproic acid is a branched-chain fatty acid and its major mechanisms of action rest on its effect on sodium currents and T-calcium channel currents, and its inhibition of GABA metabolism.[54]

Valproic acid absorption is complete but is delayed by food. It is 90% protein bound and the unbound fraction is significantly higher in the elderly. Approximately 20% of the drug is excreted as direct conjugate and the remainder is metabolised by oxidation. The median elimination half-life is 7.2 hours in young individuals but 14.9 hours in the elderly. However, clearance does not appear to differ significantly between groups. The prolonged half-life is the result of a greater volume of

distribution in the elderly.[79] At high concentrations, clearance of valproic acid is dose-dependent and there is an increase in free fraction, resulting in lower total drug concentrations than expected. Valproic acid inhibits hepatic oxidative metabolism of carbamazepine, phenobarbital, phenytoin and carbamazepine epoxide. This effect is especially relevant with phenobarbital (there is a significant increase in phenobarbital concentrations). Valproic acid inhibits phenytoin metabolism and displaces it from plasma proteins, leading to a marked increase of phenytoin concentrations.[80] Enzyme-inducing anticonvulsants reduce valproic acid plasma concentrations. Aspirin (acetylsalicylic acid) inhibits valproic acid metabolism and displaces valproic acid from its protein binding sites, increasing plasma concentrations of valproic acid.[81] Valproic acid has a synergistic pharmacokinetic and pharmacodynamic effect with lamotrigine.[82] The addition of valproic acid to a lamotrigine monotherapy regimen results in a decrease of lamotrigine clearance, the degree of inhibition of clearance being independent of the dose and concentration of valproic acid (small doses of valproic acid are enough to produce this effect).[83]

The efficacy of valproic acid has been shown in many comparative monotherapy trials. Valproic acid has been compared with phenytoin,[73] with phenytoin, carbamazepine and phenobarbital (similar efficacy but significantly better tolerated than phenobarbital),[59] with phenytoin and carbamazepine (similar efficacy and tolerability),[60] and with carbamazepine.[61,62] In all comparative trials with carbamazepine, valproic acid had similar efficacy and tolerability except in the Veterans Affairs Study,[62] in which valproic acid appeared as effective as carbamazepine for the treatment of generalised tonic-clonic seizures, but was less effective for partial seizures and had significantly more adverse events.

The major adverse effects of valproic acid are tremor, alopecia, bodyweight gain and gastrointestinal complaints.[84] A few cases of reversible parkinsonism have also been observed, and this effect may be relevant in the elderly.[85] Recently, hyperandrogenism and polycystic ovaries in women have been associated with valproic acid,[86] although the relevance of this effect in the elderly is unknown. Valproic acid does not appear to affect cognitive function in elderly patients.[87,88] A single-blind, randomised study has compared cognitive performance of elderly patients with new-onset epilepsy treated with phenytoin or valproic acid in monotherapy.[89] No significant differences were found between the drugs or compared with pretreatment status.

8.6 Benzodiazepines

Benzodiazepines are frequently administered as add-on medication for partial or generalised seizures. Their mechanism of action resides in being an allosteric modulator of the GABA-A receptor site. Diazepam, midazolam and lorazepam are frequently used in acute situations both as intravenous and oral forms. Clobazam and clonazepam are most often used in the oral form as long-term therapy.

Benzodiazepines have good bioavailability and are highly protein bound (up to 95%). Diazepam and clobazam are oxidised and lorazepam is glucuronised in the liver. Benzodiazepines are not inducers of microsomal enzymes.[90] Clearance is 98% hepatic and is reduced (up to 40%) for diazepam, midazolam and clobazam in elderly men.[91] Diazepam half-life can increase in the elderly up to 100 hours because of a reduction of clearance.[46] Although the aging process is associated with small changes in the kinetics of lorazepam, these are not clinically significant.[92] In the elderly, changes in pharmacodynamics may be more important than pharmacokinetic alterations to explain their high sensitivity to CNS-related adverse events.

Use of benzodiazepines in aged patients can predispose to symptoms such as drowsiness, ataxia, fatigue, confusion, weakness, dizziness, vertigo, reversible dementia, depression, impairment of intellect, agitation, auditory and visual hallucinations, paranoid ideation, panic, and delirium.[93] A prospective cohort study carried out in 418 inpatients who had normal cognitive function on admission to hospital showed that nearly 11% developed cognitive impairment and 5% developed

delirium.[94] Benzodiazepine use accounted for 29% of cases of cognitive impairment.[94] In addition, the features of benzodiazepine withdrawal in the elderly may differ from those seen in young patients. Withdrawal symptoms include confusion and disorientation, which often are not preceded by milder reactions such as anxiety, insomnia and perceptual changes. Problems due to both adverse reactions and benzodiazepine withdrawal may easily be overlooked in elderly patients with multiple morbidities.[95] Finally, benzodiazepine use is associated with an increased risk of falls in the elderly[96] and an increase in the sedative adverse events of other CNS depressant drugs (phenobarbital, tricyclic antidepressants, opioids).

8.7 Lamotrigine

Lamotrigine is effective in partial and generalised seizures, including Lennox-Gastaut syndrome.[97-99] Its mechanism of action is through presynaptic blockade of sodium-dependent channels and inhibiting glutamate release.

Lamotrigine has good absorption and linear dose response and is 55% protein bound. It is extensively metabolised, mainly through glucuronidation, and lacks enzyme-inducing properties.[100] The glucuronidation pathway has a large capacity and is little affected by aging. Lamotrigine is excreted predominantly by the kidney and has linear kinetics. The elimination half-life is 24 hours, but is halved by concomitant enzyme-inducing anticonvulsants or doubled by valproic acid.[83,101] No other significant interactions have been observed. No significant pharmacokinetic changes have been observed in the elderly.[100] Renal impairment appears to have little effect on plasma concentrations,[102] unless severe.

The efficacy of lamotrigine has been well established by four comparative monotherapy trials: one with phenytoin and three with carbamazepine. A double-blind trial in patients with partial and generalised new-onset seizures showed that lamotrigine and phenytoin were similarly effective.[74] Lamotrigine appeared to be better tolerated and with a lower incidence of CNS adverse effects.[74] However, discontinuation due to skin rash was twice as high with lamotrigine as with phenytoin, probably because of the rapid titration used in this trial. Two other trials compared lamotrigine with carbamazepine.[103,104] Efficacy was similar, but lamotrigine was associated with fewer adverse events. The fourth trial compared lamotrigine and carbamazepine in monotherapy in the elderly.[66] This is the only monotherapy trial ever attempted in an elderly population. It was a multicentre, double-blind trial in 150 elderly patients (with a mean age of 77 years) with new-onset epilepsy comparing the efficacy and tolerability of carbamazepine and lamotrigine. Efficacy (measured as time to first seizure) was similar, but a significantly greater percentage of lamotrigine-treated patients remained seizure-free during the last 16 weeks of treatment (lamotrigine 39%, carbamazepine 21%). The rate of withdrawal due to adverse events was significantly greater in the group treated with carbamazepine (42%) than in the lamotrigine group (18%). Lamotrigine-treated patients had lower rates of rash (3 *vs* 19%) and less frequent somnolence (12 *vs* 29%) than patients treated with carbamazepine. Overall, significantly more patients continued treatment with lamotrigine than with carbamazepine (71 *vs* 42%) for the duration of the study.[66]

Lamotrigine-associated adverse events are relatively mild, especially in the cognitive sphere.[105] Most adverse events are CNS related (dizziness, asthenia, somnolence and headache). A high frequency of rash and relatively frequent cases of Stevens-Johnson syndrome (1 per 1000 patients) were observed in clinical trials, especially in children.[106] The frequency of rash is related to the rate of titration, the initial dose and concomitant use of valproic acid.[107] A retrospective study showed that after lowering the starting dose and slowing the titration schedule in response to the manufacturer's recommendation, there was a significant reduction in the incidence of serious rash, from 1.5% (12 of 805) to 0% (0 of 245). However, there was no reduction in the overall incidence of lamotrigine-related rash, with 63 of 805 (8%) before and 23 of 245 (9%) after the recommendation.[108] The oc-

currence of rashes in the elderly population appears to be lower than in adults or children, although no direct comparison has been done.

8.8 Tiagabine

Tiagabine increases the amount of the inhibitory neurotransmitter GABA in the synaptic cleft. It reduces the neuronal and astrocytic reuptake by blocking two of the four GABA reuptake systems: GAT-1 and GAT-3.[109]

Tiagabine has 100% bioavailability, does not induce microsomal enzymes and its absorption and clearance are linear.[109,110] It is 96% bound to plasma proteins, but this appears to be of little relevance in patients.[111] Tiagabine is metabolised in the liver through the CYP3A, and thus its plasma concentration is reduced by microsomal enzyme inducers.[110] Moderate or severe liver disease increases free tiagabine plasma concentration and prolongs half-life.[112] Plasma half-life of tiagabine is 7 to 9 hours in patients not receiving CYP-inducing drugs and 2 to 4 hours in those treated with inducer anticonvulsants.[113] In patients not receiving CYP-inducing tiagabine can be given twice daily. Advanced age or renal insufficiency do not appear to cause a significant reduction in tiagabine clearance.[110,111] Tiagabine does not interact with theophylline, warfarin or digoxin.

The efficacy of tiagabine has been demonstrated in several add-on trials[114] and monotherapy trials in refractory patients.[115] No add-on trial or monotherapy trial comparing tiagabine with other anticonvulsants in refractory or new-onset partial seizures has been published, except in a difficult-to-evaluate abstract comparing tiagabine with carbamazepine.[116]

In clinical trials tiagabine has been generally well tolerated.[117] Most adverse events are CNS related (dizziness, sedation, ataxia, difficulty in attention-concentration or tremor) and appear to be dose related.[118] Several case reports have associated nonconvulsive status epilepticus with tiagabine use.[119-121] However, combined data from add-on trials showed a status frequency of 0.6% in tiagabine-treated patients compared with 0.7% in placebo-treated patients.[109] The effect of tiagabine on cognition has been evaluated in a conversion to monotherapy study in refractory patients with partial seizures.[122] It was observed that patients attaining monotherapy with tiagabine had positive changes in several neuropsychological tests.

8.9 Topiramate

Topiramate is a broad spectrum anticonvulsant that is effective both in partial and generalised seizures and in Lennox-Gastaut syndrome. It is active at sodium-dependent channels and may modulate GABA-A receptors.[123]

Topiramate is well absorbed, has low protein binding (less than 17%) and linear pharmacokinetics, and is not extensively metabolised. Its excretion is through the kidney and it has a half-life of 19 to 25 hours, allowing twice daily administration.[123] Carbamazepine and phenytoin reduce the plasma concentration of topiramate by 50%, and topiramate increases phenytoin concentration by 25%.

The efficacy of topiramate is well documented in both partial and generalised seizures in add-on therapy.[124,125] Pooled analysis of five add-on trials in refractory partial seizures showed that 41% of patients had a 50% reduction of seizures, 19% had a 75% reduction and 4% were seizure free.[126] No comparative monotherapy trials in new-onset epilepsy have been published. There also are no controlled trials in the elderly. A retrospective analysis of 50 patients aged >50 years drawn from five double-blind trials showed similar efficacy to that in younger adults.[126]

In addition to CNS-related adverse events, that are common to all anticonvulsants, several others are relevant to topiramate: anorexia and bodyweight loss that can be pronounced; renal calculi in 1 to 2% of patients; and cognitive adverse events.[125,127] In a randomised study in healthy adults who were given topiramate, lamotrigine or gabapentin, it was observed that those taking topiramate had statistically significant declines on measures of attention and word fluency whereas the other two anticonvulsant groups had no performance changes. This effect was seen throughout the 4-week period of the

trial.[127] These deleterious cognitive adverse events have also been found in patients with epilepsy (younger than 60 years) in a randomised, observer-blinded, parallel-group clinical trial with valproic acid or topiramate given as first-line add-on therapy to treatment with carbamazepine.[128] Word-recognition learning and auditory verbal learning were significantly impaired in patients taking topiramate compared with those taking valproic acid. There are no data on possible cognitive adverse events in the elderly.

8.10 Gabapentin

Gabapentin is active in both partial and generalised seizures but not in generalised epilepsies. Its mechanism of action is at present unknown, although there is evidence that it increases brain GABA.[129]

Gabapentin is absorbed through a saturable L-amino acid transport system, so that the percentage of drug absorbed decreases with increasing dose. Absorption at doses of less than 1800 mg/day is 70%, whereas at doses over 3600 mg/day it is 35%. Concomitant use of antacids can reduce its absorption by 20%. Gabapentin is not protein bound and is not metabolised. It is 100% eliminated unchanged through renal excretion.[130] No drug interactions have been observed. Elimination half-life is 6 to 9 hours, and 3 times daily administration is recommended. However, recent data have shown that gabapentin can be administered twice daily.[131]

Efficacy has been demonstrated in add-on trials on refractory partial seizures.[132-134] The efficacy and tolerability of gabapentin have also been studied in one trial in recent-onset partial epilepsy.[135] This was a dose-ranging trial with three blinded gabapentin arms at different dosages (300, 900 and 1800 mg/day) and one open-label carbamazepine arm. Gabapentin at doses of 900 and 1800 mg/day had similar efficacy.[135] The completion rate for the carbamazepine group (37%) was similar to that of the gabapentin 900mg (39%) and 1800mg (38%) groups. Patients receiving carbamazepine had a higher withdrawal rate because of adverse events compared with the gabapentin 900mg and 1800mg groups. Retention on treatment (exit event plus adverse event withdrawal rate) was similar for 1800 mg/day gabapentin and carbamazepine but was better for 900 mg/day gabapentin. However, as the carbamazepine arm was open, direct comparisons of efficacy or tolerability are not appropriate.

The most common adverse events associated with gabapentin are somnolence, dizziness, ataxia and fatigue.[136,137] Bodyweight increase has also been observed.[138] Gabapentin appears to have little cognitive effect in elderly patients: a recent randomised, crossover study in healthy elderly persons comparing carbamazepine with gabapentin has shown that both AEDs have a modest detrimental influence on cognition compared with no drug.[139] However, patients receiving gabapentin had a slightly (but significantly) lower cognitive effect than those receiving carbamazepine.

8.11 Oxcarbazepine

Oxcarbazepine is a keto derivative of carbamazepine with efficacy in partial and generalised seizures. Its main mechanism of action appears to be through blocking voltage-sensitive sodium channels. It also has an effect on potassium channels that might be clinically important.[140]

Oxcarbazepine is well absorbed and completely biotransformed by a first-pass effect to the monohydroxy derivative 10-hydroxycarbazepine (MHD), an active metabolite responsible for its action. Both oxcarbazepine and MHD bind to plasma proteins to a moderate degree (30 and 67% respectively. Oxcarbazepine and MHD have linear pharmacokinetics. Metabolism of oxcarbazepine is very different from that of carbamazepine. It undergoes metabolic reduction followed by glucuronidation instead of oxidation and there is no epoxide formation or autoinduction.[141] Oxcarbazepine does not appear to induce the CYP enzymes in general, although it does induce CYP3A4, which is responsible for the metabolism of estrogens and the dihydropyridine calcium channel antagonists (e.g. nifedipine, felodipine). Oxcarbazepine also inhibits CYP2C19.[142] Clearance of oxcarbazepine is 99% hepatic, but MHD is eliminated in the

urine. The plasma half-life of oxcarbazepine ranges from 1 to 6 hours and that of MHD from 8 to 10 hours.[142,143] However, the kinetics of oxcarbazepine do not appear to be affected by impaired liver or kidney function.[142] Oxcarbazepine interacts with phenytoin (increasing its plasma concentration by up to 40%) and with phenobarbital (increasing by 15%). It is usually necessary to reduce the phenytoin dose when titrating oxcarbazepine. Anticonvulsants with enzyme-inducing properties reduce plasma oxcarbazepine concentrations by 30 to 40%. A moderate (≈25%) decrease of serum concentrations of nifedipine, felodipine and lamotrigine[144] and a more pronounced increase of citalopram and antipsychotic plasma concentrations can occur when oxcarbazepine is added to these drugs.[145,146] A significantly higher maximum concentration, higher area under the curve parameters, and a lower elimination rate constant have been observed in the elderly. These observations are in line with a smaller renal clearance of MHD in the elderly group.[147] In a clinical situation, these age-related differences are not likely to have important implications.[147]

Double-blind trials in refractory partial seizures have shown that up to 50% of patients have a 50% reduction of seizures.[148,149] A relatively high number of these patients attained freedom from seizures during the trials (up to 12%).[149] Oxcarbazepine is the newer anticonvulsant that has been most extensively studied in monotherapy, and several double-blind trials on new-onset epilepsy (partial and generalised seizures) have been undertaken. Oxcarbazepine (600 to 2400 mg/day) has been compared with carbamazepine, valproic acid, phenytoin and low doses of oxcarbazepine (300 mg/day).[150] Comparison with carbamazepine has shown that oxcarbazepine is similarly effective but significantly better tolerated.[65] A trial comparing oxcarbazepine with phenytoin showed similar efficacy, but the number of premature discontinuations due to adverse experiences was significantly less for oxcarbazepine, although there was no significant difference between the groups with respect to the total number of premature discontinuations.[151] Another trial conducted to compare oxcarbazepine and valproic acid showed similar efficacy and tolerability.[152] It is important to note that all of these trials were conducted in populations aged <65 years, so no specific data on the elderly are available.

The most common adverse effects with oxcarbazepine are related to the CNS (drowsiness, fatigue, dizziness) and digestive system (nausea) and usually appear transitorily at the initiation of treatment. The frequency of rash necessitating oxcarbazepine withdrawal in monotherapy trials has been 3.8%, but no cases of Stevens-Johnson syndrome have been related to the drug.[153] About one-third of patients with hypersensitivity to carbamazepine have cross-reaction to oxcarbazepine.[154] Hyponatraemia occurs more frequently with oxcarbazepine than with carbamazepine.[67,155] Sodium plasma levels <135 mmol/L have been observed in 24.5% of treated patients and <125 mmol/L in 2.7%.[156] In most cases hyponatraemia is asymptomatic. Reduction of dose and fluid intake restriction usually revert sodium levels to normal. Hyponatraemia occurs more frequently in patients comedicated with diuretics, desmopressin, nonsteroidal anti-inflammatory agents, and carbamazepine, and in patients with nephropathy. In the elderly, severe hyponatraemia (<125 mmol/L) has been observed with greater frequency (7.3%) than in younger populations.[156] Sodium levels should be measured in patients at risk or with symptoms likely to be related to hyponatraemia (somnolence, nausea, vomiting, headache, confusion, etc.).[156] Oxcarbazepine appears not to be associated with cognitive impairment. A double-blind study in healthy volunteers using relatively low doses of oxcarbazepine (600 mg/day) showed improvement in attention, alertness and psychomotor speed.[157]

8.12 Zonisamide

Zonisamide is a broad spectrum anticonvulsant that is useful in treating partial, myoclonic seizures[158] and infantile spasms.[159] It is believed that zonisamide exerts its action through blocking voltage-sensitive sodium and T-type calcium channels.[160]

Zonisamide is well absorbed, extensively metabolised, and mostly excreted through urine. It does not exhibit inducing or inhibitory effects on the hepatic microsomal system or have autoinduction. It has linear pharmacokinetics. Protein binding is between 50 and 60%. Plasma half-life is long (50 to 60 hours),[160] but a shorter half-life has been observed in patients treated with phenytoin and carbamazepine (27 to 36 hours).[161] No significant interactions with lamotrigine[162] or valproic acid have been observed.[163]

In patients with partial onset refractory seizures the percentage of responders is about 30%, with 6.2% achieving freedom from seizures.[164,165] Small monotherapy studies have been done mostly in paediatric populations.[166] No large trials in adults or elderly with new-onset epilepsy have been published.

The most common adverse events are fatigue, somnolence, dizziness and ataxia.[164] Kidney stones have been reported to occur in 2.6% of patients treated in Europe and North America, compared with 0.2% in Japanese patients.[167] Zonisamide treatment is associated with a statistically significant 8% mean increase from baseline of serum creatinine compared with placebo. This is probably related to an effect on the glomerular filtration rate. The impact of this effect in the elderly is unknown.

8.13 Levetiracetam

The mechanism of action of levetiracetam is currently unknown.[168] It has been shown to be effective in partial seizures and there is preliminary evidence for its effectiveness in generalised seizures.

Levetiracetam has nearly 100% bioavailability, has minimal protein binding. and 66% of the dose is excreted unchanged.[169] Levetiracetam is hydrolysed in several tissues including blood cells, but not in the liver, giving rise to an inactive metabolite. The half-life is 6 to 8 hours and is not dose dependent. Although half-life is short, clinically there is evidence of pharmacodynamic activity for up to 30 hours from a single dose, so that twice daily administration is possible.[170] In the elderly, half-life is increased to 10 to 11 hours.[169] Hepatic disease does not alter the pharmacokinetics of levetiracetam. Half-life is extended in patients with renal impairment in relation to a reduction in renal clearance of 35 to 60%.[169] Haemodialysis reduces the plasma concentrations. Levetiracetam dos not have significant interactions with other anticonvulsants, digoxin or warfarin.[171]

Levetiracetam has shown efficacy in patients with refractory partial seizures.[172-174] The responder rate has reached 42% and up to 8% of the patients became seizure free.[172] There are no published trials in monotherapy in new-onset epilepsy.

Major adverse events associated with levetiracetam are CNS related (somnolence, dizziness, asthenia and headache). Tolerance during long-term administration has been observed in animal models. Levetiracetam is not associated with cognitive dysfunction.[175]

8.14 Felbamate

Felbamate has shown efficacy in localisation-related epilepsy and Lennox-Gastaut syndrome.[176,177] Pharmacokinetic studies showed that elderly patients require lower initial dosage and slower dose titration than younger patients.[178] After felbamate had been marketed for a few years, several cases of aplastic anaemia and liver failure were seen and these led to restricted use.[179-181] Felbamate is not indicated in elderly patients unless no other medication is available.[182]

8.15 Vigabatrin

Vigabatrin (gamma-vinyl-GABA) increases brain GABA and enhances GABA-ergic transmission by being an irreversible inhibitor of the GABA metabolising enzyme GABA transaminase.[183] It has shown effectiveness in localisation-related epilepsies and infantile spasms.[184,185]

Vigabatrin has high bioavailability and low protein binding, is not metabolised in the liver, and is renally excreted unchanged. The half-life is 5 to 8 hours, but because of the irreversible inhibition of GABA transaminase, a much longer effective half-life is suspected. Once or twice daily administration can be used.[186] Vigabatrin has low interaction

potential, but decreases phenytoin concentration in about 20% of patients.[187] In the elderly, half-life is lengthened by reduction of renal excretion. This is relevant only if creatinine clearance is reduced to <60 ml/min.

In monotherapy trials in patients with new-onset partial seizures vigabatrin has been less effective than carbamazepine, but better tolerated.[64,188] In one trial vigabatrin had no detrimental effects on cognitive functions; on the contrary, improvement in memory and flexibility in mental processing was observed.[64]

Recent reports have shown the occurrence of visual field constriction in up to 40% of patients treated with vigabatrin.[189-191] Visual field loss resulting from vigabatrin treatment does not appear to be reversible and, in some patients, can be severe.[192] In most patients the visual defect is not symptomatic.[191] The visual field defect can occur both in adults and in elderly patients.[191] The mechanism of this adverse event is unknown; however, the abnormal electroretinograms in patients indicate that retinal dysfunction in the underlying mechanism of the constriction. The precise nature of this retinal abnormality is not yet known.

8.16 Intravenous Formulations

The anticonvulsants with an intravenous form (phenytoin, fosphenytoin, valproic acid, diazepam, lorazepam, clonazepam and midazolam) are mostly used for the treatment of status epilepticus, but are also used for quick anticonvulsant loading for prevention of seizures.

Benzodiazepines (lorazepam, diazepam and clonazepam) are the first-line treatment for status epilepticus. Usually lorazepam is preferred to diazepam because of its smaller volume of distribution, leading to longer action.[193] In a recent double-blind trial, intravenous lorazepam was as effective as intravenous diazepam plus intravenous phenytoin and phenobarbital for the control of the status, for reducing the recurrence rate and decreasing the occurrence of adverse events.[194] Intravenous phenytoin alone had lower efficacy. Because of its ease of use, lorazepam is the drug of choice for first-line treatment of status epilepticus. Lorazepam pharmacokinetics show some changes in the elderly population: it has a smaller volume of distribution and its clearance is 22% reduced, but the half-life is similar.[92]

As a second-line agent, phenytoin or fosphenytoin is recommended if status epilepticus is not controlled within 5 to 7 minutes.[195] Intravenous phenytoin has been associated with fatal haemodynamic complications and serious reactions at the injection site, including skin necrosis and amputation of extremities.[196] Fosphenytoin, a phenytoin prodrug, has the same pharmacological properties as phenytoin but achieves a therapeutic level in 15 minutes as opposed to 25 minutes for phenytoin.[197] Fosphenytoin has several important advantages over phenytoin: it requires a shorter infusion time, causes less pain and burning at the infusion site, has better intravenous fluid compatibility and stability, and is well tolerated intramuscularly.[198] Moreover, fosphenytoin does not have the injection site and cardiac rhythm complications of intravenous infusions of phenytoin.[195,199]

Midazolam has also been found useful for the control of status epilepticus.[200] In the elderly, midazolam has a longer half-life (4.1 hours compared with 2.4 hours in patients <50 years) in relation to alterations in clearance and volume of distribution with age.[201,202]

Intravenous valproic acid does not produce significant changes in blood pressure or pulse and is well tolerated in elderly patients.[203,204] Elderly patients with cardiovascular instability are candidates for intravenous valproic acid, although its efficacy in status epilepticus has not been demonstrated.

9. Guidelines for Treatment

9.1 When to Initiate Treatment

This is perhaps the most difficult decision to take and, in the elderly, there is scarce information on the risk of recurrent seizures after having had one or two. Before initiating a treatment, several aspects have to be taken into account:

1. That the patient has seizures. It is common for epilepsy to be misdiagnosed in the elderly.[205]
2. That the first seizure that leads to the diagnosis is truly the first one. Careful history examination often reveals the presence of previous undisclosed seizures. This is especially true in patients with complex partial seizures that may have been misdiagnosed until a secondarily generalised seizure leads the patient to the emergency room. In fact, in one study 37% of the patients assessed because of a first seizure had previous seizures and another 33% of the patients had previous acute symptomatic seizures.[206] Thus, only a third of the patients have had a truly first seizure on the first evaluation.
3. That the seizures are unprovoked. Acute symptomatic seizures are more frequent in the elderly population[4,21] and they do not need long-term anticonvulsant treatment.
4. That seizures have an effect on the quality of life. Treating epilepsy in the elderly has to acknowledge both the detriment in quality of life that seizures might impose on the patient and the effect of long-term anticonvulsant medications. Undoubtedly, seizures or the fear of them have a profound impression on elderly patients, depression and anxiety being the most common consequences.[207,208] In addition, seizures in the elderly, specially if they are associated with falls, have a greater risk of injury because of lower bone mineral density, concomitant diseases, or the social situation (living alone).[205,209,210]
5. The comorbid situation and comedication, frequently found in the elderly population. In an ongoing prospective clinical trial in the elderly, associated disease affected more than half of the population (high blood pressure, previous stroke, cardiac disease, diabetes mellitus or history of cancer).[211] A convulsive seizure in patients with coronary disease or arrhythmia may pose a threatening vital risk.

What is the recurrence risk of a first unprovoked seizure? Hauser et al.[212] conducted a prospective epidemiological study for a mean duration of 4 years on seizure recurrence after having had a first one. Recurrence risks were estimated to be 14, 29 and 34% at 1, 3 and 5 years after the first episode. A history of previous neurological insult (remote symptomatic) was associated with a 2.5-fold increased risk of recurrence. Depending on clinical features, recurrence risk at 5 years after a first seizure could range from 23 to 80%. In other studies the presence of localisation-related epilepsy,[213] cerebral lesion[206,212,214] or an abnormal (epileptiform) EEG[215] were also factors associated with higher recurrence rate. In another study that included both unprovoked seizures and acute symptomatic seizures, the risk of recurrence after a first seizure in patients aged >60 years was shown to be 83% by 36 months.[213] Similarly, in the First Seizure Trial, seizure recurrence tended to be more frequent in elderly patients than in adults after a first seizure (39.1 *vs* 24.9%).[215] However, a lower recurrence rate (25%) after first seizure has been observed in a prospective study in the elderly,[216] the recurrence being comparable to that of younger populations.[217]

Most authors would agree that after two seizures anticonvulsant treatment is warranted. The risk of having a third unprovoked seizure is 73% at 4 years and, among those with a third unprovoked seizure, the risk of a fourth is 76%.[206]

Should an elderly patient be treated with an anticonvulsant after a first unprovoked seizure? This is probably one of the most controversial questions and there is probably not a universal answer. In the large prospective First Seizure Trial, patients untreated after the first seizure had a significantly higher risk of relapse than the treated ones (51 *vs* 25%).[215] However, in the study by Hauser et al.,[212] treatment with anticonvulsant medication was not associated with a decrease in recurrence risks.

Our personal view is that treating after a first unprovoked seizure can be acceptable in the elderly, especially in those with risk factors for higher recurrence (presence of lesion, epileptiform EEG, identifiable aetiology, or being of focal onset). The decision should be individualised.

9.2 Appropriate Dose

It is believed that elderly patients with epilepsy have a favourable response to low doses of anti-

convulsants.[53,218] There are, however, few prospective studies analysing the effectiveness and tolerability of anticonvulsants in the elderly population. A retrospective study of 73 elderly patients treated with classic anticonvulsants showed that seizure freedom could be achieved in 61% of patients with low doses of an anticonvulsant (mean daily doses of phenytoin 248mg, carbamazepine 320mg and valproic acid 571mg).[219] Another recent prospective study comparing lamotrigine and carbamazepine in the elderly has confirmed that low doses are often effective and well tolerated (median dose of lamotrigine 100 mg/day and median dose of carbamazepine 400 mg/day).[66] These studies and clinical experience suggest that doses or plasma concentration on the lower limit of the 'adult' therapeutic range are appropriate in the elderly population.[219]

In general, anticonvulsant titration in the elderly should be done at a slower rate to avoid adverse events related to changes in pharmacokinetic behaviour or special sensitivity.

9.3 Anticonvulsant of Choice

No single anticonvulsant can be recommended as the most effective and best tolerated in the aging population. Choosing a first-line anticonvulsant should include consideration of its efficacy, tolerability, pharmacokinetic profile, concomitant medications and medical problems, and availability and price (tables I and II). As has been stated above, only one double-blind trial comparing anticonvulsants (lamotrigine and carbamazepine) has been carried out in the elderly.[66] In fact, clinical trials are difficult to perform in the elderly. In an ongoing prospective study in new-onset epilepsy in the elderly, 403 patients from 736 were excluded during screening.[220] The most common exclusion reasons were unstable medical disorder (23.3%), inability to give consent (20.3%) and questionable compliance (19.6%).[220]

When both the pharmacokinetic data on anticonvulsants and their effectiveness in monotherapy are analysed, it appears that three drugs could be used as first-line monotherapy in the elderly: valproic acid, lamotrigine and gabapentin. Despite the potential toxicity and pharmacokinetic shortcomings, carbamazepine is also a possible first choice because of the long-term experience that most clinicians have with it. Drug selection among these four anticonvulsants depends largely on individual characteristics. Phenobarbital and primidone should not be used as first-line therapy because of their potential cognitive adverse events. Phenytoin does not appear as a good first choice because of its quite unfavourable pharmacokinetic profile. Oxcarbazepine has a high risk of hyponatraemia. Topiramate, tiagabine and zonisamide can be used as second-line agents in add-on therapy. Vigabatrin and felbamate should be used only in exceptional circumstances because of their major potentially severe adverse events. Benzodiazepines should rarely if ever be used for long-term treatment in the elderly.

An ongoing study by the Veterans Affairs Cooperative 428 Study Group is prospectively comparing the response to treatment of elderly patients with untreated epilepsy. Patients are randomised to carbamazepine (600 mg/day), gabapentin (1500 mg/day) or lamotrigine (150 mg/day).[211] The preliminary data presented on 280 patients show a high degree of intolerance to anticonvulsants. CNS toxicity is found in 66% of the patients and the drop-out rate at 12 months has been 52.2%. Data on efficacy are pending.

9.4 Concomitant Medications and Diseases

Elderly patients are frequently treated with multiple concomitant medications, giving rise to potentially complex pharmacokinetic interactions to anticonvulsants. In addition, the elderly population may be more susceptible to potentially epileptogenic medications such as intravenous penicillins, intravenous cephalosporins, imipenem, ciprofloxacin, theophylline, pethidine (meperidine), cyclosporin, clozapine, haloperidol, tricyclic antidepressants, amfebutamone (bupropion), lithium or iodine contrast. Concomitant disease is very frequent in the elderly and complicates treatment. In the ongoing Veterans Affairs Study, 64.4% had hyperten-

sion, 52.7% history of stroke, 48.8% cardiac disease, 26.6% diabetes mellitus and 22.5% history of cancer.[211]

9.5 Monotherapy and Polytherapy

Most elderly patients can successfully be treated with monotherapy. Only when monotherapy fails, may combination therapy be tried in an attempt to improve effectiveness. In general, polytherapy based on mechanisms of action has been postulated to enhance effectiveness, but could lead to important interactions depending on the drugs used.[221] Combining a sodium channel blocker (e.g. carbamazepine) with a drug enhancing GABA-ergic inhibition could be appropriate. Also, combining two GABA mimetic drugs or combining an AMPA antagonist with an *N*-methyl-D-aspartate antagonist may enhance efficacy, but tolerability is reduced.[221] Combining two sodium channel blockers seems less appropriate. However, knowledge of the pathophysiology of seizures and of the exact mechanisms of action of anticonvulsants is incomplete. Moreover, the effectiveness or tolerability of polytherapy in aging populations is yet to be demonstrated.

9.6 Response to Treatment

It is widely believed that seizures in the elderly respond easily to anticonvulsants. However, there is little solid information behind this assumption. Data available on the response to classic anticonvulsants in new-onset epilepsy in the elderly have been obtained from a retrospective analysis from the Veterans Affairs trials.[58,62] At a follow-up of 24 months, over 65% of the elderly patients remained seizure free compared with less than 40% of younger patients (data from Krämer[222]), implying a population less prone to refractoriness. On the other hand, in the National General Practice Study of Epilepsy (a large population-based prospective study to assess prognosis of patients with newly diagnosed epilepsy) it was shown that the probability of a 5-year remission is poorer in the elderly than in younger populations.[223] Finally, a prospective study in elderly patients with new-onset epilepsy showed a favourable prognosis (72% entered remission within the first year).[216] Thus, at present it is unclear if epilepsy in the elderly has a different treatment prognosis from that in adults. Comparative epidemiological studies are needed to address this issue.

10. Conclusions

The incidence of epilepsy in the elderly is rising. Diagnosis tends to be difficult because of the multiple confounding associated medical problems. Both convulsive and nonconvulsive seizures are more threatening in the elderly because of the risk of injury and reduced independence. Response to anticonvulsant treatment is generally good and most aged patients can be seizure free. Anticonvulsant treatment, however, is associated with multiple difficulties in relation to changes in pharmacokinetics associated with age, particular susceptibility of the elderly to CNS-acting drugs, and concomitant disease and medications. Unfortunately, there is a paucity of controlled data on the treatment of epilepsy in the elderly and further studies are needed to improve our approach to treatment in this population.

Acknowledgements

Both Dr Arroyo and Dr Kramer have received travel or research grants, cunsultancy fees or have been on the speakers panels of the major pharmaceutical companies that produce anticonvulsants Novatis, Parke Davis/Pfizer, Desitin, Glaxo-Wellcome (now GlaxoSmithKline), Aventis/Hoechst Marion Rousell, Jansen-Cilag, Novo Nordisk, Sanofi-Synthelabo and UCB.

References

1. Annegers JF, Hauser WA, Lee R-J, et al. Incidence of acute symptomatic seizures in Rochester, Minnesota, 1935-1984. Epilepsia 1995; 36: 327-33
2. Loiseau J, Loiseau P, Duché B, et al. A survey of epileptic disorders in southwest France: seizures in elderly patients. Ann Neurol 1990; 27: 232-7
3. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 1993; 34: 453-68
4. Wallace H, Shorvon S, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. Lancet 1998; 352: 1970-3

5. Forsgren L, Bucht G, Eriksson S, et al. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. Epilepsia 1996; 37: 224-9
6. Olafsson E, Hauser WA, Ludvigsson P, et al. Incidence of epilepsy in rural Iceland: a population-based study. Epilepsia 1996; 37: 951-5
7. Hauser WA, Annegers JF, Kurland AH. Prevalence of epilepsy in Rochester, Minnesota: 1940-1980. Epilepsia 1991; 32: 429-45
8. de la Court A, Breteler MMB, Meinardi H, et al. Prevalence of epilepsy in the elderly: the Rotterdam study. Epilepsia 1996; 37: 141-7
9. Keranen T, Sillanpaa M, Riekkinen PJ. Distribution of seizure types in an epileptic population. Epilepsia 1988; 29: 1-7
10. Fisher RS, Webber WR, Lesser RP, et al. High-frequency EEG activity at the start of seizures. J Clin Neurophysiol 1992; 9: 441-8
11. Gram L, Alving J, Sagild JC, et al. Juvenile myoclonic epilepsy in unexpected age groups. Epilepsy Res 1988; 2 (2): 137-40
12. Grunewald RA, Panayiotopoulos CP. Diagnosing juvenile myoclonic epilepsy in an elderly patient. Seizure 1994; 3: 239-41
13. Nishiura N, Oiwa T. Epilepsy above 70 years of age – four cases with spike and wave complex. Folia Psychiatr Neurol Jpn 1979; 33 (3): 263-8
14. Loiseau J, Crespel A, Picot MC, et al. Idiopathic generalized epilepsy of late onset. Seizure 1998; 7: 485-7
15. Li X, Breteler MM, de Bruyne MC, et al. Vascular determinants of epilepsy: the Rotterdam Study. Epilepsia 1997; 38: 1216-20
16. Berges S, Moulin T, Berger E, et al. Seizures and epilepsy following strokes: recurrence factors. Eur Neurol 2000; 43: 3-8
17. Arboix A, Garcia-Eroles L, Massons JB, et al. Predictive factors of early seizures after acute cerebrovascular disease. Stroke 1997; 28: 1590-4
18. Reith J, Jorgensen HS, Nakayama H, et al. Seizures in acute stroke: predictors and prognostic significance. The Copenhagen Stroke Study. Stroke 1997; 28: 1585-9
19. Burn J, Dennis M, Bamford J, et al. Epileptic seizures after a first stroke: the Oxfordshire community stroke project. BMJ 1997; 315: 1582-7
20. So EL, Annegers JF, Hauser WA, et al. Population-based study of seizure disorders after cerebral infarction. Neurology 1996; 46: 350-5
21. Faught E, Peters D, Bartolucci A, et al. Seizures after primary intracerebral hemorrhage. Neurology 1989; 39: 1089-93
22. Shinton RA, Gill JS, Zezulka AV, et al. The frequency of epilepsy preceding stroke,case-control study in 230 patients. Lancet 1987; 11-3
23. Hesdorffer DC, Hauser WA, Annegers JF, et al. Severe, uncontrolled hypertension and adult-onset seizures: a case- control study in Rochester, Minnesota. Epilepsia 1996; 37: 736-41
24. Hesdorffer DC, Hauser WA, Annegers JF, et al. Dementia and adult-onset unprovoked seizures. Neurology 1996; 46: 727-30
25. Hauser WA, Morris ML, Heston LL, et al. Seizures and myoclonus in patients with Alzheimer's disease. Neurology 1986; 36: 1226-30
26. Lowry JK, Snyder JJ, Lowry PW. Brain tumors in the elderly: recent trends in a Minnesota cohort study. Arch Neurol 1998; 55: 922-8
27. Ng SK, Hauser WA, Brust JC, et al. Alcohol consumption and the risk of new onset seizure. N Engl J Med 1988; 319: 666-73
28. Harden CL, Rosenbaum DH, Daras M. Hyperglycemia presenting with occipital seizures. Epilepsia 1991; 32: 215-20
29. Askenasy JJ, Streifler M, Carasso R. Moderate nonketotic hyperglycemia – a cause of focal epilepsy. Report of two cases and review of literature. Eur Neurol 1977; 16: 51-61
30. Spitz MC, Bainbride JL, Ramsay ER, et al. Observations on the delay in the diagnosis of seizures in the elderly [abstract]. Epilepsia 2000; 41 Suppl. 7: 109
31. Drury I, Beydoun A. Pitfalls of EEG interpretation in epilepsy. Neurol Clin 1993; 11: 857-81
32. Santamaria J, Chiappa KH. The EEG of drowsiness in normal adults. J Clin Neurophysiol 1987; 4: 327-82
33. Drury I, Beydoun A. Interictal epileptiform activity in elderly patients with epilepsy. Electroencephalogr Clin Neurophysiol 1998; 106: 369-73
34. Drury I, Selwa LM, Schuh LA, et al. Value of inpatient diagnostic CCTV-EEG monitoring in the elderly. Epilepsia 1999; 40: 1100-2
35. van Donselaar CA, Geerts AT, Schimsheimer RJ. Idiopathic first seizure in adult life: who should be treated? BMJ 1991; 302: 620-3
36. Schreiner A, Pohlmann-Eden B, Schwartz A, et al. Epileptic seizures in subcortical vascular encephalopathy. J Neurol Sci 1995; 130: 171-7
37. Taveras JM. Nuclear magnetic resonance imaging. AJR Am J Roentgenol 1982; 139 (2): 406-7
38. Hesdorffer DC, Logroscino G, Cascino G, et al. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. Neurology 1998; 50: 735-41
39. Coeytaux A, Jallon P, Galobardes B, et al. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). Neurology 2000; 55: 693-7
40. Rumbach L, Sablot D, Berger E, et al. Status epilepticus in stroke: report on a hospital-based stroke cohort. Neurology 2000; 54: 350-4
41. Waterhouse EJ, Vaughan JK, Barnes TY, et al. Synergistic effect of status epilepticus and ischemic brain injury on mortality. Epilepsy Res 1998; 29: 175-83
42. Allcock LM, O'Shea D. Diagnostic yield and development of a neurocardiovascular investigation unit for older adults in a district hospital. J Gerontol A Biol Sci Med Sci 2000 Aug; 55 (8): M458-62
43. Tatum WO, Ross J, Cole AJ. Epileptic pseudodementia. Neurology 1998; 50: 1472-5
44. Zucconi M, Ferini-Strambi L. NREM parasomnias: arousal disorders and differentiation from nocturnal frontal lobe epilepsy. Clin Neurophysiol 2000 Sep; 111 Suppl. 2: S129-35
45. Fakhoury T, Abou-Khalil B, Newman K. Psychogenic seizures in old age: a case report. Epilepsia 1993 Nov-Dec; 34 (6): 1049-51
46. Ochs HR, Otten H, Greenblatt DJ, et al. Diazepam absorption: effects of age, sex, and Billroth gastrectomy. Dig Dis Sci 1982; 27 (3): 225-30
47. Greenblatt DJ. Reduced serum albumin concentration in the elderly: a report from the Boston Collaborative Drug Surveillance Program. J Am Geriatr Soc 1979; 27 (1): 20-2
48. Koyama H, Sugioka N, Uno A, et al. Age-related alteration of carbamazepine-serum protein binding in man. J Pharm Pharmacol 1999; 51: 1009-14
49. Woodhouse KW, Wynne HA. Age-related changes in liver size and hepatic blood flow. The influence on drug metabolism in the elderly. Clin Pharmacokinet 1988; 15 (5): 287-94
50. Nolan L, O'Malley K. Prescribing for the elderly. Part I: sensitivity of the elderly to adverse drug reactions. J Am Geriatr Soc 1988; 36 2): 142-9
51. Pryor FM, Ramsay DA, Rowan AJ, et al. Diagnostic, demographic and retention issues in managing seizures in older adults [abstract]. Neurology 2000; 54 Suppl. 3: A84-5

52. Geddes JW, Ulas J, Brunner LC, et al. Hippocampal excitatory amino acid receptors in elderly, normal individuals and those with Alzheimer's disease: non-N-methyl-D-aspartate receptors. Neuroscience 1992; 50: 23-34
53. Faught E. Epidemiology and drug treatment of epilepsy in elderly people. Drugs Aging 1999; 15: 255-69
54. Macdonald RL, Kelly, KM. Antiepileptic drug mechanisms of action. Epilepsia 1995: 32 Suppl. 2; S2-12
55. Bertilsson L, Tomson T, Tybring G. Pharmacokinetics: time-dependent changes – autoinduction of carbamazepine epoxidation. J Clin Pharmacol 1986; 26: 459-62
56. Westenberg HG, van der Kleijn E, Oei TT, et al. Kinetics of carbamazepine and carbamazepine-epoxide, determined by use of plasma and saliva. Clin Pharmacol Ther 1978; 23: 320-8
57. Hockings N, Pall A, Moody J, et al. The effects of age on carbamazepine pharmacokinetics and adverse effects. Br J Clin Pharmacol 1986; 22: 725-8
58. Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. N Engl J Med 1985; 313: 145-51
59. Heller AJ, Chesterman P, Elwes RDC, et al. Phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed adult epilepsy: a randomised comparative monotherapy trial. J Neurol Neurosurg Psychiat 1995; 58: 44-50
60. Callaghan N, Kenny RA, O'Neill B, et al. A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. J Neurol Neurosurg Psychiat 1985; 48: 639-44
61. Richens A, Davidson DL, Cartlidge NE, et al. A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy. Adult EPITEG Collaborative Group. J Neurol Neurosurg Psychiat 1994; 57: 682-7
62. Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. N Engl J Med 1992; 327: 765-71
63. Troupin A, Moretti Ojemman L, Halpern L, et al. Carbamazepine – a double-blind comparison with phenytoin. Neurology 1977; 27: 511-9
64. Kalviainen R, Aikia M, Saukkonen AM, et al. Vigabatrin vs carbamazepine monotherapy in patients with newly diagnosed epilepsy. A randomized, controlled study. Arch Neurol 1995; 52: 989-96
65. Dam M, Ekberg R, Loyning Y, et al. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. Epilepsy Res 1989; 3: 70-6
66. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. Epilepsy Res 1999; 37: 81-7
67. Van Amelsvoort T, Bakshi R, Devaux CB, et al. Hyponatremia associated with carbamazepine and oxcarbazepine therapy: a review. Epilepsia 1994; 35: 181-8
68. Takayanagi K, Hisauchi I, Watanabe J, et al. Carbamazepine-induced sinus node dysfunction and atrioventricular block in elderly women. Jpn Heart J 1998; 39: 469-79
69. Umstead GS, Morales M, McKercher PL. Comparison of total, free, and salivary phenytoin concentrations in geriatric patients. Clin Pharm 1986; 5: 59-62
70. Bauer LA, Blouin RA. Age and phenytoin kinetics in adult epileptics. Clin Pharmacol Ther 1982; 31 (3): 301-4
71. Anderson GD, Pak C, Doane KW, et al. Revised Winter-Tozer equation for normalized phenytoin concentrations in trauma and elderly patients with hypoalbuminemia. Ann Pharmacother 1997; 31: 279-84
72. Reidenberg MM, Odar-Cederlof I, von Bahr C, et al. Protein binding of diphenylhydantoin and desmethylimipramine in plasma from patients with poor renal function. N Engl J Med 1971; 285 (5): 264-7
73. Turnbull DM, Howel D, Rawlins MD, et al. Which drug for the adult epileptic patient: phenytoin or valproate? BMJ Clin Res Ed 1985; 290: 815-9
74. Steiner TJ, Dellaportas CI, Findley LJ, et al. Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double- blind comparison with phenytoin. Epilepsia 1999; 40: 601-7
75. Duncan JS, Shorvon SD, Trimble MR. Effects of removal of phenytoin, carbamazepine, and valproate on cognitive function. Epilepsia 1990; 31: 584-91
76. Tjellesen L, Gotfredsen A, Borg J, et al. Relationship between local and total body bone mineral in epileptic patients and normal subjects. Clin Physiol 1983; 3: 359-64
77. Christiansen C, Rodbro P, Lund M. Incidence of anticonvulsant osteomalacia and effect of vitamin D: controlled therapeutic trial. BMJ 1973; 4: 695-701
78. Martines C, Gatti G, Sasso E, et al. The disposition of primidone in elderly patients. Br J Clin Pharmacol 1990; 30 (4): 607-11
79. Bryson SM, Verma N, Scott PJ, et al. Pharmacokinetics of valproic acid in young and elderly subjects. Br J Clin Pharmacol 1983; 16 (1): 104-5
80. Duncan JS, Patsalos PN, Shorvon SD. Effects of discontinuation of phenytoin, carbamazepine, and valproate on concomitant antiepileptic medication. Epilepsia 1991; 32: 101-15
81. Fleitman JS, Bruni J, Perrin JH, et al. Albumin-binding interactions of sodium valproate. J Clin Pharmacol 1980; 20: 514-7
82. Pisani F, Oteri G, Russo MF, et al. The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. Epilepsia 1999; 40: 1141-6
83. Kanner AM, Frey M. Adding valproate to lamotrigine: a study of their pharmacokinetic interaction. Neurology 2000; 55: 588-91
84. Corman CL, Leung NM, Guberman AH. Weight gain in epileptic patients during treatment with valproic acid: a retrospective study. Can J Neurol Sci 1997; 24: 240-4
85. Armon C, Shin C, Miller P, et al. Reversible parkinsonism and cognitive impairment with chronic valproate use. Neurology 1996; 47: 626-35
86. Isojarvi JI, Rattya J, Myllyla VV, et al. Valproate, lamotrigine, and insulin-mediated risks in women with epilepsy. Ann Neurol 1998; 43: 446-51
87. Read CL, Stephen LJ, Stolarek IH, et al. Cognitive effects of anticonvulsant monotherapy in elderly patients: a placebo-controlled study. Seizure 1998; 7: 159-62
88. Prevey ML, Delaney RC, Cramer JA, et al. Effect of valproate on cognitive functioning. Comparison with carbamazepine. The Department of Veterans Affairs Epilepsy Cooperative Study 264 Group. Arch Neurol 1996; 53: 1008-16
89. Craig I, Tallis R. Impact of valproate and phenytoin on cognitive function in elderly patients: results of a single-blind randomized comparative study. Epilepsia 1994; 35: 381-90
90. Rupp W, Badian M, Christ O, et al. Pharmacokinetics of single and multiple doses of clobazam in humans. Br J Clin Pharmacol 1979; 7 Suppl. 1: 51S-7

91. Bernus I, Dickinson RG, Hooper WD, et al. Anticonvulsant therapy in aged patients. Clinical pharmacokinetic considerations. Drugs Aging 1997; 10 (4): 278-89
92. Greenblatt DJ, Allen MD, Locniskar A, et al. Lorazepam kinetics in the elderly. Clin Pharmacol Ther 1979; 26 (1): 103-13
93. Lechin F, Van der Dijs B, Benaim M. Benzodiazepines: tolerability in elderly patients. Psychother Psychosom 1996; 65 (4): 171-82
94. Foy A, O'Connell D, Henry D, et al. Benzodiazepine use as a cause of cognitive impairment in elderly hospital inpatients. J Gerontol A Biol Sci Med Sci 1995; 50 (2): M99-106
95. Kruse WH. Problems and pitfalls in the use of benzodiazepines in the elderly. Drug Saf 1990; 5 (5): 328-44
96. Trewin VF, Lawrence CJ, Veitch GB. An investigation of the association of benzodiazepines and other hypnotics with the incidence of falls in the elderly. J Clin Pharm Ther 1992; 17 (2): 129-33
97. Gilliam F, Vazquez B, Sackellares JC, et al. An active-control trial of lamotrigine monotherapy for partial seizures. Neurology 1998; 51: 1018-25
98. Motte J, Trevathan E, Arvidsson JF, et al. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. Lamictal Lennox-Gastaut Study Group. N Engl J Med 1997; 337: 1807-12
99. Binnie CD, Debets RM, Engelsman M, et al. Double-blind crossover trial of lamotrigine (Lamictal) as add-on therapy in intractable epilepsy. Epilepsy Res 1989; 4: 222-9
100. Hussein Z, Posner J. Population pharmacokinetics of lamotrigine monotherapy in patients with epilepsy: retrospective analysis of routine monitoring data. Br J Clin Pharmacol 1997; 43: 457-65
101. Cohen AF, Land GS, Breimer DD, et al. Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. Clin Pharmacol Ther 1987; 42: 535-41
102. Wootton R, Soul-Lawton J, Rolan PE, et al. Comparison of the pharmacokinetics of lamotrigine in patients with chronic renal failure and healthy volunteers. Br J Clin Pharmacol 1997; 43 (1): 23-7
103. Reunanen M, Dam M, Yuen AW. A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. Epilepsy Res 1996; 23: 149-55
104. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Lancet 1995; 345: 476-9
105. Giorgi L, Gomez G, O'Neill F, et al. The tolerability of lamotrigine in elderly patients with epilepsy. Drugs Aging 2001; 18 (8): 621-30
106. Messenheimer J, Mullens EL, Giorgi L, et al. Safety review of adult clinical trial experience with lamotrigine. Drug Saf 1998; 18: 281-96
107. Messenheimer JA, Guberman AH. Rash with lamotrigine: dosing guidelines. Epilepsia 2000; 41 (4): 488
108. Wong IC, Mawer GE, Sander JW. Factors influencing the incidence of lamotrigine-related skin rash. Ann Pharmacother 1999; 33 (10): 1037-42
109. Adkins JC, Noble S. Tiagabine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of epilepsy. Drugs 1998; 55: 437-60
110. Snel S, Jansen JA, Mengel HB, et al. The pharmacokinetics of tiagabine in healthy elderly volunteers and elderly patients with epilepsy. J Clin Pharmacol 1997; 37: 1015-20
111. Samara EE, Gustavson LE, El Shourbagy T, et al. Population analysis of the pharmacokinetics of tiagabine in patients with epilepsy. Epilepsia 1998; 39: 868-73
112. Lau AH, Gustavson LE, Sperelakis R, et al. Pharmacokinetics and safety of tiagabine in subjects with various degrees of hepatic function. Epilepsia 1997; 38: 445-51
113. So EL, Wolff D, Graves NM, et al. Pharmacokinetics of tiagabine as add-on therapy in patients taking enzyme-inducing antiepilepsy drugs. Epilepsy Res 1995; 22: 221-6
114. Ben-Menachem E. International experience with tiagabine add-on therapy. Epilepsia 1995; 36 Suppl. 6: S14-21
115. Schachter SC. Tiagabine monotherapy in the treatment of partial epilepsy. Epilepsia 1995; 36 Suppl. 6: S2-6
116. Brodie MJ, Bomhof MAM, Kälviäinen R. Double-blind comparison of tiagabine and carbamazepine monotherapy in newly diagnosed epilepsy [abstract]. Epilepsia 1997; 38 Suppl. 3: 66
117. Leppik IE. Tiagabine: the safety landscape. Epilepsia 1995; 36 Suppl. 6: S10-3
118. Leppik IE, Gram L, Deaton R, et al. Safety of tiagabine: summary of 53 trials. Epilepsy Res 1999; 33: 235-46
119. Balslev T, Uldall P, Buchholt J. Provocation of non-convulsive status epilepticus by tiagabine in three adolescent patients. Eur J Paediatr Neurol 2000; 4: 169-70
120. Trinka E, Moroder T, Nagler M, et al. Clinical and EEG findings in complex partial status epilepticus with tiagabine. Seizure 1999; 8: 41-4
121. Schapel G, Chadwick D. Tiagabine and non-convulsive status epilepticus. Seizure 1996; 5: 153-6
122. Dodrill CB, Arnett JL, Shu V, et al. Effects of tiagabine monotherapy on abilities, adjustment, and mood. Epilepsia 1998; 39: 33-42
123. Garnett WR. Clinical pharmacology of topiramate: a review. Epilepsia 2000; 41 Suppl. 1: S61-5
124. Abou-Khalil B. Topiramate in the long-term management of refractory epilepsy. Topiramate YOL Study Group. Epilepsia 2000; 41 Suppl. 1: S72-6
125. Reife R, Pledger G, Wu SC. Topiramate as add-on therapy: pooled analysis of randomized controlled trials in adults. Epilepsia 2000; 41 Suppl. 1: S66-71
126. Reife RA, Pledger GW. Topiramate as adjunctive therapy in refractory partial epilepsy: pooled analysis of data from five double-blind, placebo-controlled trials. Epilepsia 1997; 38 Suppl. 1: S31-3
127. Martin R, Kuzniecky R, Ho S, et al. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. Neurology 1999; 52: 321-7
128. Aldenkamp AP, Baker G, Mulder OG, et al. A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures. Epilepsia 2000; 41 (9): 1167-78
129. Petroff OA, Rothman DL, Behar KL, et al. The effect of gabapentin on brain gamma-aminobutyric acid in patients with epilepsy. Ann Neurol 1996; 39: 95-9
130. Goa KL, Sorkin EM. Gabapentin. A review of its pharmacological properties and clinical potential in epilepsy. Drugs 1993; 46: 409-27
131. Muscas GC, Chiroli S, Luceri F, et al. Conversion from thrice daily to twice daily administration of gabapentin (GBP) in partial epilepsy: analysis of clinical efficacy and plasma levels. Seizure 2000; 9: 47-50
132. Bergey GK, Morris HH, Rosenfeld W, et al. Gabapentin monotherapy: I. An 8-day, double-blind, dose-controlled, multicenter study in hospitalized patients with refractory complex

partial or secondarily generalized seizures. The US Gabapentin Study Group 88/89. Neurology 1997; 49: 739-45
133. Beydoun A, Fischer J, Labar DR, et al. Gabapentin monotherapy: II. A 26-week, double-blind, dose-controlled, multicenter study of conversion from polytherapy in outpatients with refractory complex partial or secondarily generalized seizures. The US Gabapentin Study Group 82/83. Neurology 1997; 49: 746-52
134. The US Gabapentin Study Group No. 5. Gabapentin as add-on therapy in refractory partial epilepsy: a double blind, placebo-controlled, parallel-group study. Neurology 1993; 43: 2292-8
135. Chadwick DW, Anhut H, Greiner MJ, et al. A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. International Gabapentin Monotherapy Study Group 945-77. Neurology 1998; 51: 1282-8
136. Marson AG, Kadir ZA, Hutton JL, et al. Gabapentin for drug-resistant partial epilepsy. Cochrane Database Syst Rev 2000; (2): CD001415
137. Morris GL. Gabapentin. Epilepsia 1999; 40 Suppl. 5: S63-70
138. DeToledo JC, Toledo C, DeCerce J, et al. Changes in body weight with chronic, high-dose gabapentin therapy. Ther Drug Monit 1997; 19: 394-6
139. Martin R, Meador K, Turrentine L, et al. Comparative cognitive effects of carbamazepine and gabapentin in healthy senior adults. Epilepsia 2001; 42 (6): 764-71
140. McLean MJ, Schmutz M, Wamil AW, et al. Oxcarbazepine: mechanisms of action. Epilepsia 1994; 35: Suppl. 3: S5-9
141. Isojarvi JI, Pakarinen AJ, Rautio A, et al. Liver enzyme induction and serum lipid levels after replacement of carbamazepine with oxcarbazepine. Epilepsia 1994; 35: 1217-20
142. Lloyd P, Flesch G, Dieterle W. Clinical pharmacology and pharmacokinetics of oxcarbazepine. Epilepsia 1994; 35: Suppl. 3: S10-3
143. Baruzzi A, Albani F, Riva R. Oxcarbazepine: pharmacokinetic interactions and their clinical relevance. Epilepsia 1994; 35 Suppl. 3: S14-9
144. May TW, Rambeck B, Jurgens U. Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in epileptic patients with and without valproic acid comedication: results of a retrospective study. Ther Drug Monit 1999; 21: 175-81
145. Leinonen E, Lepola U, Koponen H. Substituting carbamazepine with oxcarbazepine increases citalopram levels. A report on two cases. Pharmacopsychiatry 1996; 29: 156-8
146. Raitasuo V, Lehtovaara R, Huttunen MO. Effect of switching carbamazepine to oxcarbazepine on the plasma levels of neuroleptics. A case report. Psychopharmacology Berl 1994; 116: 115-6
147. van Heiningen PN, Eve MD, Oosterhuis B, et al. The influence of age on the pharmacokinetics of the antiepileptic agent oxcarbazepine. Clin Pharmacol Ther 1991; 50: 410-9
148. Schachter SC, Vazquez B, Fisher RS, et al. Oxcarbazepine: double-blind, randomized, placebo-control, monotherapy trial for partial seizures. Neurology 1999; 52: 732-7
149. Barcs G, Walker EB, Elger CE, et al. Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. Epilepsia 2000; 41 (12): 1597-607
150. Beydoun A, Sachdeo RC, Rosenfeld WE, et al. Oxcarbazepine monotherapy for partial-onset seizures: a multicenter, double-blind, clinical trial. Neurology 2000; 54: 2245-51
151. Bill PA, Vigonius U, Pohlmann H, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. Epilepsy Res 1997; 27: 195-204
152. Christe W, Kramer G, Vigonius U, et al. A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. Epilepsy Res 1997; 26: 451-60
153. Shorvon S. Oxcarbazepine: a review. Seizure 2000; 9: 75-9
154. Beran RG. Cross-reactive skin eruption with both carbamazepine and oxcarbazepine. Epilepsia 1993; 34: 163-5
155. Dam M. Practical aspects of oxcarbazepine treatment. Epilepsia 1994; 35 Suppl. 3: S23-5
156. Schmidt D, Arroyo S, Baulac M, et al. Recommendations on the clinical use of oxcarbazepine in the treatment of epilepsy: a consensus view. Seizure. Acta Neurol Scand 2001; 104: 167-70
157. Curran HV, Java R. Memory and psychomotor effects of oxcarbazepine in healthy human volunteers. Eur J Clin Pharmacol 1993; 44: 529-33
158. Kyllerman M, Ben-Menachem E. Zonisamide for progressive myoclonus epilepsy: long-term observations in seven patients. Epilepsy Res 1998; 29: 109-14
159. Suzuki Y, Nagai T, Ono J, et al. Zonisamide monotherapy in newly diagnosed infantile spasms. Epilepsia 1997; 38: 1035-8
160. Kochak GM, Page JG, Buchanan RA, et al. Steady-state pharmacokinetics of zonisamide, an antiepileptic agent for treatment of refractory complex partial seizures. J Clin Pharmacol 1998; 38: 166-71
161. Ojemann LM, Shastri RA, Wilensky AJ, et al. Comparative pharmacokinetics of zonisamide (CI-912) in epileptic patients on carbamazepine or phenytoin monotherapy. Ther Drug Monit 1986; 8 (3): 293-6
162. Yamashita S, Furuno K, Moriyama M, et al. Effects of various antiepileptic drugs on plasma levels of lamotrigine, a novel antiepileptic, in rats. Pharmacology 1997; 54: 319-27
163. Tasaki K, Minami T, Ieiri I, et al. Drug interactions of zonisamide with phenytoin and sodium valproate: serum concentrations and protein binding. Brain Dev 1995; 17: 182-5
164. Schmidt D, Jacob R, Loiseau P, et al. Zonisamide for add-on treatment of refractory partial epilepsy: a European double-blind trial. Epilepsy Res 1993; 15: 67-73
165. Wilensky AJ, Friel PN, Ojemann LM, et al. Zonisamide in epilepsy: a pilot study. Epilepsia 1985; 26: 212-20
166. Kumagai N, Seki T, Yamawaki H, et al. Monotherapy for childhood epilepsies with zonisamide. Jpn J Psychiatry Neurol 1991; 45 (2): 357-9
167. Seino M, Miyazaki H, Ito T. Zonisamide. Epilepsy Res Suppl 1991; 3: 169-74
168. Genton P, Van Vleymen B. Piracetam and levetiracetam: close structural similarities but different pharmacological and clinical profiles. Epileptic Disord 2000; 2 (2): 99-105
169. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. Pharmacol Ther 2000; 85: 77-85
170. Kasteleijn-Nolst TD, Marescaux C, Stodieck S, et al. Photosensitive epilepsy: a model to study the effects of antiepileptic drugs. Evaluation of the piracetam analogue, levetiracetam. Epilepsy Res 1996; 25: 225-30
171. Browne TR, Szabo GK, Leppik IE, et al. Absence of pharmacokinetic drug interaction of levetiracetam with phenytoin in patients with epilepsy determined by new technique. J Clin Pharmacol 2000; 40 (6): 590-5
172. Ben Menachem E, Falter U. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. European Levetiracetam Study Group. Epilepsia 2000; 41 (10): 1276-83

173. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. Seizure 2000; 9: 80-7
174. Cereghino JJ, Biton V, Abou-Khalil B, et al. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. Neurology 2000; 55: 236-42
175. Neyens LG, Alpherts WC, Aldenkamp AP. Cognitive effects of a new pyrrolidine derivative (levetiracetam) in patients with epilepsy. Prog Neuropsychopharmacol Biol Psychiatry 1995; 19: 411-9
176. The Felbamate Study Group in Lennox-Gastaut Syndrome. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). N Engl J Med 1993; 328: 29-33
177. Faught E, Sachdeo RC, Remler MP, et al. Felbamate monotherapy for partial-onset seizures: an active-control trial. Neurology 1993; 43: 688-92
178. Richens A, Banfield CR, Salfi M, et al. Single and multiple dose pharmacokinetics of felbamate in the elderly. Br J Clin Pharmacol 1997; 44: 129-34
179. Kaufman DW, Kelly JP, Anderson T, et al. Evaluation of case reports of aplastic anemia among patients treated with felbamate. Epilepsia 1997; 38: 1265-9
180. O'Neil MG, Perdun CS, Wilson MB, et al. Felbamate-associated fatal acute hepatic necrosis. Neurology 1996; 46: 1457-9
181. Pennell PB, Ogaily MS, Macdonald RL. Aplastic anemia in a patient receiving felbamate for complex partial seizures. Neurology 1995; 45: 456-60
182. French J, Smith M, Faught E, et al. Practice advisory: the use of felbamate in the treatment of patients with intractable epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 1999; 52 (8): 1540-5
183. Ben-Menachem E. Vigabatrin. Epilepsia 1995; 36 Suppl. 2: S95-104
184. Beran RG, Berkovic SF, Buchanan N, et al. A double-blind, placebo-controlled crossover study of vigabatrin 2 g/day and 3 g/day in uncontrolled partial seizures. Seizure 1996; 5: 259-65
185. Fejerman N, Cersosimo R, Caraballo R, et al. Vigabatrin as a first-choice drug in the treatment of West syndrome. J Child Neurol 2000; 15: 161-5
186. Ben-Menachem E, Persson L, Mumford J. Long-term evaluation of once daily vigabatrin in drug-resistant partial epilepsy. Epilepsy Res 1990; 5: 240-6
187. Browne TR, Mattson RH, Penry JK, et al. Vigabatrin for refractory complex partial seizures: multicenter single-blind study with long-term follow-up. Neurology 1987; 37: 184-9
188. Chadwick D. Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: a multicentre randomised double-blind study. Vigabatrin European Monotherapy Study Group. Lancet 1999; 354: 13-9
189. Krauss GL, Johnson MA, Miller NR. Vigabatrin-associated retinal cone system dysfunction: electroretinogram and ophthalmologic findings. Neurology 1998; 50: 614-8
190. Miller NR, Johnson MA, Paul SR, et al. Visual dysfunction in patients receiving vigabatrin: clinical and electrophysiologic findings. Neurology 1999; 53: 2082-7
191. Kalviainen R, Nousiainen I, Mantyjarvi M, et al. Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual field defects. Neurology 1999; 53 (5): 922-6
192. Johnson MA, Krauss GL, Miller NR, et al. Visual function loss from vigabatrin: effect of stopping the drug. Neurology 2000; 55: 40-5
193. Treiman DM. Pharmacokinetics and clinical use of benzodiazepines in the management of status epilepticus. Epilepsia 1989; 30 Suppl. 2: S4-10
194. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998; 339: 792-8
195. Bleck TP. Management approaches to prolonged seizures and status epilepticus. Epilepsia 1999; 40 Suppl. 1: S59-63
196. O'Brien TJ, Cascino GD, So EL, et al. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. Neurology 1998 Oct; 51 (4): 1034-9
197. Browne TR, Kugler AR, Eldon MA. Pharmacology and pharmacokinetics of fosphenytoin. Neurology 1996 Jun; 46 (6 Suppl. 1): S3-7
198. Ramsay RE, DeToledo J. Intravenous administration of fosphenytoin: options for the management of seizures. Neurology 1996; 46: S17-9
199. Pryor FM, Gidal B, Ramsay RE, et al. Fosphenytoin: pharmacokinetics and tolerance of intramuscular loading doses. Epilepsia 2001; 42 (2): 245-50
200. Parent JM, Lowenstein H. Treatment of refractory generalized status epilepticus with continuous infusion of midazolam. Neurology 1994; 44: 1837-40
201. Harper KW, Collier PS, Dundee JW, et al. Age and nature of operation influence the pharmacokinetics of midazolam. Br J Anaesth 1985; 57: 866-71
202. Smith MT, Heazlewood V, Eadie MJ, et al. Pharmacokinetics of midazolam in the aged. Eur J Clin Pharmacol 1984; 26: 381-8
203. Sinha S, Naritoku DK. Intravenous valproate is well tolerated in unstable patients with status epilepticus. Neurology 2000; 55: 722-4
204. Venkataraman V, Wheless JW. Safety of rapid intravenous infusion of valproate loading doses in epilepsy patients. Epilepsy Res 1999; 35 (2): 147-53
205. Lühdorf K, Jensen LK, Plesner AM. Epilepsy in the elderly: incidence,social function and disability. Epilepsia 1986; 27: 135-41
206. Hauser WA, Rich SS, Lee JR, et al. Risk of recurrent seizures after two unprovoked seizures. N Engl J Med 1998; 338: 429-34
207. Baker GA, Nashef L, van Hout BA. Current issues in the management of epilepsy: the impact of frequent seizures on cost of illness, quality of life, and mortality. Epilepsia 1997; 38 Suppl. 1: S1-8
208. Jacoby A, Baker GA, Steen N, et al. The clinical course of epilepsy and its psychosocial correlates: findings from a U.K. community study. Epilepsia 1996; 37: 148-61
209. Stephen LJ, McLellan AR, Harrison JH, et al. Bone density and antiepileptic drugs: a case-controlled study. Seizure 1999; 8: 339-42
210. Finelli PF, Cardi JK. Seizure as a cause of fracture. Neurology 1989; 39: 858-60
211. Ramsay E, Rowan AJ, Pryor FM, et al. Seizures in the older patient: demographics, diagnosis, and treatment [abstract]. Epilepsia 2000; 41 Suppl. 7: 172
212. Hauser WA, Rich SS, Annegers JF, et al. Seizure recurrence after a first unprovoked seizure: an extended follow-up. Neurology 1990; 40: 1163-70
213. Hart YM, Sander JW, Johnson AL, et al. National General Practice Study of Epilepsy: recurrence after a first seizure. Lancet 1990; 336: 1271-4

214. Rocca WA, Sharbrough FW, Hauser WA, et al. Risk factors for complex partial seizures: a population-based case-control study. Ann Neurol 1987; 21: 22-31
215. First Seizure Trial Group (FIR.S.T.Group). Randomized clinical trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. Neurology 1993; 43: 478-83
216. Lühdorf K, Jensen K. Epilepsy in the elderly: prognosis. Acta Neurol Scand 1986; 74: 409-15
217. Elwes RDC, Johnson AL, Shorvon SD, et al. The prognosis for seizure control in newly diagnosed epilepsy. N Engl J Med 1984; 311: 944-77
218. Holt-Seitz A, Wirrell EC, Sundaram MB. Seizures in the elderly: etiology and prognosis. Can J Neurol Sci 1999; 26: 110-4
219. Cameron H, Macphee GJ. Anticonvulsant therapy in the elderly – a need for placebo controlled trials. Epilepsy Res 1995; 21: 149-57
220. Johnson J, Pryor FM, Ramsay RE, et al. Clinical trials: recruitment challenges in the elderly [abstract]. Epilepsia 2000; 41 Suppl. 7: 109
221. Deckers CL, Czuczwar SJ, Hekster YA, et al. Selection of antiepileptic drug polytherapy based on mechanisms of action: the evidence reviewed. Epilepsia 2000; 41 (11): 1364-74
222. Krämer G. Special features of individual antiepileptic drugs. In: Krämer G, editor. Epilepsy in the elderly. Stuttgart: Thieme Verlag, 1999: 75-103
223. Cockerell OC, Johnson AL, Sander JW, et al. Prognosis of epilepsy: a review and further analysis of the first nine years of the British National General Practice Study of Epilepsy, a prospective population-based study. Epilepsia 1997; 38: 31-46

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