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EMMI BRUUN

ANTIEPILEPTIC DRUG TREATMENT IN THE ELDERLY

Choice of initial treatment, potential interactions and seizure outcome

*Antiepileptic drug treatment in the elderly:
Choice of initial treatment, potential
interactions and seizure outcome*

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Antiepileptic drug treatment in the elderly: choice of initial treatment, potential interactions and seizure outcome

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ABSTRACT

Elderly people are more vulnerable to seizures than younger adults, because of neurodegeneration and issues created by several concomitant disorders and use of various drugs, often in combination. Treatment and selection of a suitable antiepileptic drug (AED) for treating epilepsy can be rendered difficult also by altered pharmacokinetics, AEDs' adverse effects, and potential for interactions with and between other drugs. Old age is the most common time to experience an epileptic seizure; among all age groups, elderly people exhibit the highest incidence rates for epilepsy.

Several sets of guidelines for the treatment of epilepsy have been published in recent years, but they give either very little guidance on the treatment of elderly patients or none whatsoever. Using first-generation AEDs is not highly recommended for elderly patients, because of their pharmacological profile, yet most of the elderly patients are prescribed these. While second-generation AEDs might be more suitable, since they may have fewer adverse effects and interactions with other drugs, they are not as well studied as older ones in elderly patients. Rates of seizure-freedom and responding well to AEDs tend to be higher in elderly patients than in the general adult population, but good clinical data on seizure outcomes in the elderly-patients group remain scarce.

A study was carried out to examine AED choices, outcomes, and drug interactions for patients with epilepsy aged 65 years or above. The pattern of initial prescription of AEDs was retrospectively studied in two community-dwelling cohorts, identified from the case records of Kuopio University Hospital (KUH) and nationwide register data from the Social Insurance Institution of Finland. The outcome of initial AED monotherapy in elderly patients with newly diagnosed epilepsy was investigated in terms of the cumulative probabilities of ≥ 2 - and ≥ 5 -year complete seizure remission.

Valproic acid and carbamazepine were the most common initial AEDs among the elderly patients (with 49% and 31% of prescriptions, respectively) at KUH. The corresponding AEDs at national level were valproic acid and oxcarbazepine. Sixty-four per cent of the patients used the initial AED as monotherapy and 86% of patients were treated successfully with some form of monotherapy. The estimated cumulative probability of achieving ≥ 2 years' remission was 83%, and that for ≥ 5 years of remission was 79%. Four per cent of the patients developed refractory epilepsy. Hypertension was the most common co-morbid condition (67%). The frequency of excessive polypharmacy increased with advancing age. Of the patients started on carbamazepine, 32% had at least one clinically significant interaction with drugs used for other conditions, and 31% had two or more. The most

common drugs with potential interactions with carbamazepine were dihydropyridine calcium-channel blockers, statins, warfarin, and psychotropic drugs.

The study showed that the prognosis for seizures in elderly patients with newly diagnosed epilepsy is good and that most patients can be successfully treated with the first AED. Comorbid conditions and pharmacokinetic drug–drug interactions are quite commonplace in elderly patients with newly diagnosed epilepsy but can be controlled via rational drug choices and through prediction of the possible drug–drug interactions.

National Library of Medicine Classification: WT 166, WL 385, WB 330, QV 37.5, QV 56, QV 85

Medical Subject Headings: Aged; Epilepsy; Seizures; Incidence; Probability; Drug Interactions; Drug Therapy, Combination; Polypharmacy; Carbamazepine; Valproic Acid; Comorbidity; Treatment Outcome; Prognosis

Bruun, Emmi

Epilepsian lääkehoidon erityispiirteet ikääntyneillä: ensimmäisen lääkehoidon valinta, potentiaaliset interaktiot ja kohtauksettomuuden saavuttaminen

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TIIVISTELMÄ

Hermoston rappeutumisen, useiden liitännäissairauksien ja muiden lääkkeiden käytön vuoksi iäkkäät ovat nuorempaa väestöä alttiimpia saamaan epileptisiä kohtauksia. Epilepsian hoito ja lääkkeen valinta vanhuksilla on hankalaa iän myötä muuttuneen farmakokinetiikan, lääkkeiden haittavaikutusten ja lääkeaineinteraktioiden runsauden vuoksi. Epileptisen kohtauksen saamisen todennäköisyys on suurin iäkkäillä; epilepsian ilmaantuvuus on suurin vanhimmilla ikäluokilla verrattuna nuorempiin aikuisiin.

Epilepsian hoitoon on julkaistu laajasti erilaisia hoitosuosituksia aikuisväestölle, mutta iäkkäille potilaille näissä ei ole hoito-ohjeita. Ensimmäisen polven epilepsialääkkeitä ei nykyisin suositella käytettäväksi iäkkäille potilaille niiden epäedullisen farmakologisen profiilin vuoksi, mutta silti ne ovat eniten käytettyjä lääkkeitä kyseisessä ryhmässä. Toisen polven lääkkeet saattaisivat olla parempia vaihtoehtoja verrattuna ensimmäisen polven lääkkeisiin, koska niillä on vähemmän haittavaikutuksia ja interaktioita muiden lääkkeiden kanssa, mutta niistä on vain vähän tutkimustietoa epilepsiaa sairastavilla iäkkäillä potilailla. Vaste epilepsialääkehoitoon on yleensä iäkkäillä parempi verrattuna nuorempaan väestöön, mutta kattavia kliinisiä tutkimuksia hoidon tehosta vanhuksilla ei ole montaa.

Tämän tutkimuksen tavoitteena oli tutkia ensimmäisen lääkehoidon valintaa, tehoa ja interaktioita muun lääkehoidon kanssa epilepsiaa sairastavilla iäkkäillä yli 65-vuotiailla potilailla. Tutkimusaineistona käytettiin Kuopion yliopistollisen sairaalan potilaskertomuksista kerättyä materiaalia ja Suomen Kansaneläkelaitoksen rekisterin kansallista aineistoa. Kohtauksettomuuden saavuttamista iäkkäillä potilailla tutkittiin kumulatiivisen ≥ 2 tai ≥ 5 vuoden kohtausremission saavuttamisella.

Kuopion yliopistollisen sairaalan tutkimusaineistossa valproaatti (49%) ja karbamatsepiini (31%) olivat yleisimmin käytetyt ensimmäiset epilepsian lääkehoidot iäkkäillä potilailla. 64% pystyttiin hoitamaan onnistuneesti ensimmäisellä valitulla lääkkeellä ja 86% ylipäätensä yhden lääkkeen avulla. 4% potilaista ei saavuttanut hoitovastetta lääkehoidolla eli he sairastuivat vaikeahoitoseen epilepsiaan. 83% potilaista saavutti ≥ 2 ja 79% ≥ 5 vuoden kumulatiivisen kohtausremission. Verenpainetauti oli yleisin sairastettu liitännäissairaus tutkimusaineistossa. Todennäköisyys huomattavaan monilääkehoitoon kasvoi potilaan ikääntyessä. Karbamatsepiinia ensimmäisenä monoterapialääkkeenä käyttäneistä 32%:lla oli yksi ja 31%:lla kaksi tai enemmän kliinisesti merkitseviä yhteisvaikutuksia muun lääkityksen kanssa. Yleisimmin yhteisvaikutuksia karbamatsepiinin kanssa aiheuttavia lääkkeitä olivat kalsiumkanavan salpaajat, statiinit, varfariini ja psykotrooppiset lääkkeet.

Tämän tutkimuksen perusteella kohtausten ennuste iäkkäillä potilailla on hyvä ja useimmat saavat hyvän hoitovasteen ensimmäisestä lääkehoidosta. Komorbiditeetit ja lääkeineteraktiot muiden lääkkeiden kanssa ovat yleisiä, mutta kuitenkin kontrolloitavissa järkevillä lääkeainevalinnoilla ja tulevien interaktioiden ennakkoinnilla.

Luokitus: WT 166, WL 385, WB 330, QV 37.5, QV 56, QV 85

Yleinen Suomalainen asiasanasto: vanhukset; epilepsia; lääkehoito; hoitovaste; sairauskohtaukset; monilääkehoito; polyfarmasia; karbamatsepiini; valproaatti; komorbiditeetti; liitännäistaudit; yhteisvaikutukset; ennusteet

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Savonlinna, May 2017

Emmi Bruun

List of the original publications

This dissertation is based on the following original publications:

- I Bruun E, Virta L J, Kälviäinen R and Keränen T. Choice of the first anti-epileptic drug in elderly patients with newly diagnosed epilepsy: A Finnish retrospective study. *Seizure* 31: 27-32, 2015.
- II Bruun E, Kälviäinen R, and Keränen T. Outcome of initial antiepileptic drug treatment in elderly patients with newly diagnosed epilepsy. *Epilepsy research* 127: 60-65, 2016.
- III Bruun E, Virta L J, Kälviäinen R and Keränen T. Co-morbidity and clinically significant interactions between antiepileptic drugs and other drugs in elderly patients with newly diagnosed epilepsy. *Submitted*.

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Abbreviations

AED	Antiepileptic drug	LEV	Levetiracetam
AED-PDI	Potential drug-drug interactions with antiepileptic drugs	LTG	Lamotrigine
EEG	Electroencephalography	MRI	Magnetic resonance imaging
CBZ	Carbamazepine	MS	Multiple sclerosis
GBP	Gabapentin	NGPSE	National general practice study of epilepsy
GFR	Glomerular filtration rate	OXC	Oxcarbazepine
CT	Computerized tomography	PHT	Phenytoin
GAD	Glutamic acid decarboxylase	PB	Phenobarbital
CYP	Cytochrome P450	SANAD	Standard and new antiepileptic drugs study
GAD-Abs	Anti-glutamic acid decarboxylase antibodies	SFINX	Swedish, Finnish, INteraction X-referencing
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase	SII	The Social Insurance Institution of Finland
HR	Hazard ratio	SLE	Systemic lupus erythematosus
IBE	International Bureau for Epilepsy	SUDEP	Sudden unexplained death in epilepsy patients
ILAE	International League Against Epilepsy	TPM	Topiramate
KUH	Kuopio University Hospital	VPA	Valproic acid

1 Introduction

Epilepsy is one of the most common neurological disorders in the elderly (Groselj et al. 2005). Old age is the most common period for appearance of the first epileptic seizure (Bergey 2004; Brodie & French 2000; Brodie & Stephen 2007; Brodie et al. 2009; Cloyd et al. 2006; Fosgren et al. 2005; Krämer 2001; Read 1998; Stephen et al. 2006); among all age groups, incidence rates of epilepsy are highest in the elderly (Cloyd 2005; Fosgren et al. 2005; Günter 2001; Hauser et al. 1993; Kutluay et al. 2003; Olafsson et al. 2005; Leppik & Birnbaum 2010). The most common causes of epilepsy in the elderly are cerebrovascular disorders, neurodegenerative diseases (dementia), and central nervous system tumours (Cloyd 2005; Van Cott 2002).

Elderly patients may be more vulnerable to adverse effects and interactions of antiepileptic drugs (AEDs) when compared with younger adults (Austin & Abdulla 2013; Günter 2001; Stephen & Brodie 2000). Until recent years, the first-generation AEDs (phenytoin, phenobarbital, valproic acid, and carbamazepine) have been the most commonly used AED choice among elderly patients with epilepsy (Leppik 2007). Second-generation AEDs have been suggested to be preferable over these older AEDs for possibly offering less adverse effects and interactions (Sabers & Gram 2000; Stephen & Brodie 2000; Willmore 2000). The selection and application of AEDs for the elderly is made complex, however, by altered pharmacokinetics and pharmacodynamics, comorbidities, polypharmacy, physiological changes, and concomitant functional impairment (Collins et al. 2006; Glauser et al. 2013; Stephen & Brodie 2000; Stephen et al. 2006; Leppik et al. 2012; Willmore 1996).

Several sets of guidelines for the treatment of epilepsy have been published in the past few years, but they give either very little or no guidance on the treatment of elderly patients with epilepsy (Glauser et al. 2013; Kälviäinen et al. 2014; Osseman et al. 2006; Pugh et al. 2011). Response to AEDs tends to be better and the seizure-freedom frequency higher in elderly patients than among the general adult population (Arain & Abou-Khalil 2009; Beghi et al. 2009; Brodie & Stephen 2007; Faught 1999), probably because the former represent less lesional epileptogenicity and genetic predisposition than younger patients do (Stephen et al. 2006). Complete seizure control is estimated to occur in 70% of elderly patients thus treated (Brodie & French 2000).

The study described here was designed to investigate the AED choices for patients with epilepsy of age 65 or over, along with the associated outcome and interactions.

2 Review of the Literature

2.1 DEFINITION OF EPILEPSY

According to definitions by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE), an **epileptic seizure** is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al. 2005; 2014). Presentation of a seizure depends on the location of onset in the brain; seizures can affect sensory, motor, and autonomic function and influence consciousness, emotional state, memory, cognition, and/or behaviour (Fisher et al. 2005).

Epilepsy is characterised by an enduring predisposition to generate epileptic seizures (qualification under the definition requires at least one actual epileptic seizure to occur) and by the neurobiological, cognitive, psychological, and social consequences of this condition (Fisher et al. 2005). Enduring alteration in the brain increases the likelihood of future seizures; a single epileptic seizure due to this abnormality in the brain would indicate epilepsy, but a single epileptic seizure in a normal brain would not.

In everyday clinical practice, however, diagnosis of epilepsy usually requires at least two unprovoked seizures, >24 hours apart (Fisher et al. 2005; 2014). The ILAE endorses the recommendation, made by a task force, of changing the practical definition in consideration of special circumstances that do not meet the two-unprovoked-seizures criterion, such that epilepsy is considered to be a disease of the brain demonstrated by any of the following conditions: 1) at least two unprovoked (or reflex) seizures, occurring >24 hours apart; 2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and 3) diagnosis of an epilepsy syndrome (Fisher et al. 2014).

Refractory epilepsy is defined by the ILAE (Kwan et al. 2010) as a failure to achieve sustained seizure-freedom by adequate trial of two tolerated, appropriately chosen and used AED schedules (whether as monotherapy or in combination). Either at least 12 months' seizure-freedom or a seizure-free period with a duration of at least three times the longest inter-seizure interval prior to starting a new intervention would need to be observed.

Epilepsy is considered to be **resolved** for individuals who either had an age-dependent epilepsy syndrome but are now past the associated age or have remained seizure-free for the last 10 years and off anti-seizure medicines for at least the last five; this status implies that the person no longer has epilepsy, although it may return (Fisher et al. 2014).

2.2 THE EPIDEMIOLOGY OF EPILEPSY – PREVALENCE, INCIDENCE AND AETIOLOGY

Globally, epilepsy affects 65 million people (Moshe et al. 2015). The cumulative lifetime risk of epilepsy in industrialised countries is 3%, and that of unprovoked seizures is 4% (McHugh & Delanty 2008). In the Nordic countries, the prevalence rate of epilepsy is 3.6–5.3/1,000 in children and 5.5–6.3/1,000 in adults (Eriksson & Koivikko 1997; Forsgren 1992; Keränen et al. 1989). Similar prevalence rates have been reported for other European countries (in children 5/1,000 and in adults 6/1,000), with age-specific prevalence varying within the range 5.3–6.4/1,000 in adults and being 3.2/1,000 among people aged 70 years or more (Forsgren 1992). The number of children and adolescents in Europe with active epilepsy is estimated at 0.9 million, the corresponding figure for ages 20–64 is 1.9 million, and that for ages 65 and above is 0.6 million (Forsgren et al. 2005).

The mean annual incidence of epilepsy in adults in Finland has been reported as 0.2/1,000 (Keränen et al. 1989). Estimated incidence rates cited for epilepsy in Europe are 0.7/1,000 among children and adolescents, 0.3/1,000 in adults between 20 and 64 years, and 1/1,000 for those age 65 or above (Forsgren et al. 2005). Incidence of epilepsy is reported to have decreased in the Finnish population between 1986 (0.7 in 1,000) and 2002 (0.5 in 1,000) in both men and women (Sillanpää et al. 2006), with the figure decreasing among children and adults but rising among the elderly (defined as those 65 and above). Either the incidence was slightly greater in males than females or there were only minor differences between the sexes (Forsgren 1992; Forsgren et al. 2005; Keränen et al. 1989). In children, the incidence was higher in girls than boys (Forsgren et al. 2005).

The most commonplace aetiology for epilepsy in adults is cerebrovascular disease, especially ischaemic stroke (Forsgren et al. 2005); see Figure 1. Also, epilepsy is frequently associated with neurodegenerative diseases, with the most common of these being Alzheimer's disease and vascular dementia (Forsgren et al. 1996; Olafsson et al. 1996; Oun et al. 2003; Sander et al. 1990). Special characteristics of elderly patients are discussed in greater depth later in the dissertation.

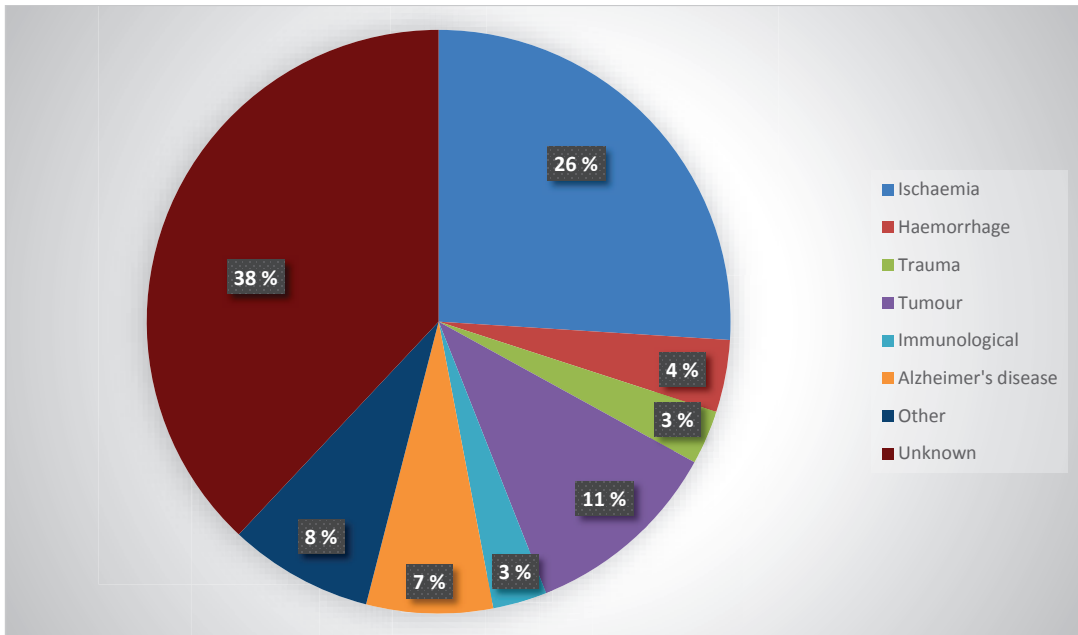


Figure 1. The aetiology of unprovoked seizures in adults, from a population-based prospective study of epileptic seizures in adults aged >17 years ($n = 563$) (see Forsgren et al. 1996).

2.3 CLASSIFICATION OF EPILEPTIC SEIZURES

The ILAE published its proposed classification of epileptic seizures in 1981 and epilepsy syndromes in 1989. Today, the clinical classification is based on modern neuroimaging, genomic technologies, and concepts from molecular biology, so the ILAE's Commission on Classification and Terminology has revised its suggested concepts, terms, and approaches for classifying seizures and forms of epilepsy accordingly (Berg et al. 2010). Figure 2 represents the ILAE's new 'roadmap' for the relevant classification of epilepsies for discussion (Scheffer et al. 2016).

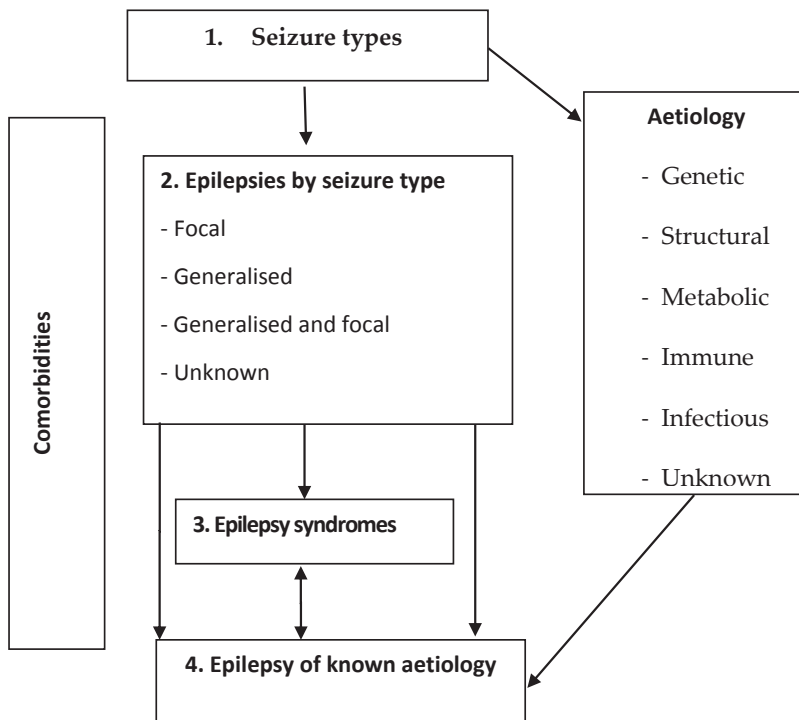


Figure 2. A framework for epilepsy classification (modified from work by Scheffer et al. 2016).

Generalised epileptic seizures are conceptualised as originating at some location within the brain and rapidly engaging bilaterally distributed networks, which may include cortical and subcortical structures but not necessarily the entire cortex (Berg et al. 2010). Seizures can be asymmetric. Generalised seizures can be assigned to subclasses: tonic-clonic, absence, myoclonic, clonic, tonic, and atonic. **Focal epileptic seizures** are conceptualised as originating within networks limited to one hemisphere and may be discretely localised or more widely distributed. Ictal onset is consistent with preferential propagation patterns that can involve the contralateral hemisphere.

The distinction previously drawn among partial seizures (between ‘complex partial’ and ‘simple partial’) has been abandoned and replaced with the notions of focal motor/sensory and focal dyscognitive seizures, in a reflection of today’s fuller insight into the pathogenesis of seizures (Berg et al. 2010; Malkan & Beran 2014). An **acute symptomatic seizure** is defined as secondary to substance (including alcohol) abuse or withdrawal or either caused by an acute illness only or linked to psychogenic non-epileptic seizures (Beghi et al. 2010). A diagnosis should be documented within 24 hours on the basis of specific biochemical or haematological abnormalities. Also, seizures are considered acute symptomatic if they occur within the first seven days of cerebrovascular disease.

Instead of ‘idiopathic’, ‘symptomatic’, and ‘cryptogenic’, the terms ‘genetic’, ‘structural’, ‘metabolic’, ‘immunological’, or ‘infectious’; and ‘unknown’, respectively, are recommended to denote the underlying cause (Berg et al. 2010; Scheffer et al. 2016). **Genetic epilepsy** is the direct result of a known or presumed genetic defect in which seizures are the core symptom of the disorder. In cases of **structural epilepsy**, there is a distinct other structural condition or disease that has been demonstrated to be associated with an increased risk of development of epilepsy. Structural lesions may be found with acquired disorders such as stroke, trauma, and infection. Finally, ‘**unknown cause**’ denotes the nature of the root cause not yet being known. This new classification scheme was developed in response to a more refined understanding of the underlying causes of epilepsy in comparison to knowledge in earlier decades (Malkan & Beran 2014).

Epilepsies themselves can be grouped into electroclinical syndromes, distinctive constellations, structural-metabolic epilepsies, and epilepsies of unknown cause (Berg et al. 2010). **Electroclinical syndromes** are displayed by those patients with a group of clinical entities that are reliably identified by a cluster of electroclinical characteristics. **Distinctive constellations** encompass the entities that are not specifically electroclinical syndromes but represent clinically distinctive constellations based on specific lesions or other causes. Epilepsies attributed to and organised on the basis of **structural-metabolic** causes include those secondary to specific structural or metabolic lesions or conditions wherein there is no particular electroclinical pattern evident. Finally, **epilepsies of unknown cause** cover the epilepsies that used to be referred to as cryptogenic.

2.4 TREATMENT WITH ANTIEPILEPTIC DRUGS

Antiepileptic drug treatment is usually started after more than one well-documented seizure has occurred (Brodie 2005; Brodie & French 2000; Iyer & Marson 2014). Patients whose electroencephalography (EEG) has shown epileptic discharges or who exhibit an underlying structural abnormality visible in brain imaging constitute an exception; these patients may be treated after a single seizure (Brodie 2005; Kälviäinen et al. 2014; Stern 2006) after considering the the risk of seizure recurrence versus weight of the possible adverse effects of AED treatment (Krumholz et al. 2015). Immediate AED treatment is likely to reduce the recurrence risk within the first 2 years but not the long-term prognosis for seizure remission.

The main goal for the treatment is to maintain a normal lifestyle via complete seizure control with minimal adverse effects (Brodie 2005; Brodie & French 2000; Tomson 2004). There is no clear first-choice drug or first add-on therapy for epilepsy, but monotherapy as the initial treatment is preferred in general (Noe 2011; Privitera 2011), because usually it is effective enough and polytherapy may have more adverse effects (Deckers 2002; Ortinski & Meador 2004). The initial AED treatment is usually selected on the basis of electroclinical diagnosis of seizure type (Azar & Abou-Khalil 2008; Stern 2009). Many further factors should be considered also, such as the AEDs' mechanism of action, comorbidities, comedication, age, teratogenic potential, adherence to treatment, and the tolerability of the AED (Asconapé 2010; Stein & Kanner 2009; Stephen & Brodie 2012).

The **first-generation AEDs** (phenytoin, carbamazepine, valproic acid, and phenobarbital) share many frequently occurring dose-related adverse effects, among them headaches, dizziness, diplopia, fatigue, and ataxia (Brodie & Dichter 1996; Brodie & French 2000). Pharmacokinetic interactions with these AEDs are commonplace; all of the first-generation AEDs except valproic acid induce the cytochrome P450 (CYP) enzyme system in the liver, thereby reducing the effectiveness of various lipid-soluble drugs, such as oral contraceptives, anticoagulants, antiarrhythmic agents, and immunosuppressants. The **second-generation AEDs** (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and pregabalin) generally have a more favourable and predictable pharmacokinetic profile and fewer interactions (Asconapé 2010; Privitera 2011), but none of them have shown superior efficacy when compared to first-generation AEDs for the treatment of focal or generalised seizures (French & Gazzolla 2013; Kwan & Brodie 2003; Tomson 2004). In addition, there are fewer data on their use as first-line treatment for epilepsy, relative to first-generation AEDs. This issue may lead to AED treatment being initiated with first-generation drugs while second-generation ones are used as adjunctive therapy (Iyer & Marson 2014; Mohanraj & Brodie 2003). The most common adverse events of second-generation AEDs are dose-related nausea, headaches, dizziness, and occasional tiredness (Bergin & Connolly 2002; Brodie & French 2000). Tables 1 and 2 summarise the pharmacological properties and clinical characteristics of the most commonly used AEDs.

The decision to discontinue AED treatment is usually more difficult than that to begin the treatment (Stern 2006). There is no consensus on the amount of seizure-free time that is optimal before withdrawal of treatment should be attempted, but at least five years of remission is recommended for adults (Brodie & French 2000). Some forms of generalised seizures, such as absence seizures in children, are less likely to recur. The probability of remaining seizure-free without treatment is greatest for people who experienced few seizures before treatment commenced, were placed on monotherapy, have been seizure-free for many years, and showed normal results in a neurological examination and no structural abnormalities revealed by brain imaging. Any relapses usually occur during or after the first year following discontinuation of AED treatment, and the risk of relapse remains increased until two years from the therapy's withdrawal (Braun & Schmidt 2014). In cases of failure to achieve complete seizure control via AEDs, epilepsy surgery (especially for patients with mesial temporal lobe epilepsy) or vagus nerve stimulation must be considered (Noe 2011; Stern 2009).

Table 1. Pharmacological properties of the most commonly used AEDs

AED	Active metabolites	Absorption (bioavailability %)	Protein binding (% bound)	Elimination half-life (hours)	Maximum plasma concentration (hours)	Volume of distribution (l/kg)
Carbamazepine	Carbamazepine-10,11-epoxide 9-hydroxymethyl-10-carbamoyl acridan	Slow (75–80)	70–80	8–24	6–20	0.8
Clobazam	N-desmethyl-clobazam	Rapid (90–100)	87–90	10–30	0.5–4	-
Gabapentin	-	Slow (60)	<3	6–9	2–3	57.7
Lamotrigine	-	Rapid (95–100)	55	22–36	2.5	0.92–1.22
Levetiracetam	-	Rapid (95–100)	<10	7–8	1.3	0.5–0.7
Oxcarbazepine	10-monohydroxy-carbamazepine	Rapid (95–100)	40	8–10	1–3	12
Phenytoin	-	Slow (85–90)	90–93	9–40	4–8	0.5–0.8
Pregabalin	-	Rapid (90–100)	0	6	1	0.56
Valproic acid	-	Rapid (100)	88–92	7–17	3–5	0.15
AED	Enzyme inducer /inhibitor	Clearance	Steady state (days)	Elimination without change (%)	Routes of elimination	Target serum concentration (mg/l)
Carbamazepine	Inducer	0.01–0.02 l/kg/hour	5–7	3	Hepatic metabolism, active metabolite	4–12
Clobazam	Inhibitor	-	-	Low	Hepatic metabolism, active metabolite	None
Gabapentin	Neither	GFR correlated	-	100	No metabolism, renal excretion	-
Lamotrigine	Neither	39 ml/min	14–28	10	Glucuronidation	4–18
Levetiracetam	Neither	0.96 ml/min/kg	2	66	Nonhepatic hydrolysis, renal excretion	-
Oxcarbazepine	Inducer in high doses, inhibitor in lower doses	2.4 l/kg/hour	-	<1	Hepatic conversion to active moiety	-
Phenytoin	Inducer	0.015–0.065 l/kg/hour	>5	Low	Saturable hepatic metabolism	10–20
Pregabalin	Neither	GFR correlated	1–2	90–99	No metabolism, renal excretion	-
Valproic acid	Inhibitor	0.010–0.015 l/kg/hour	4–7	<3	Hepatic metabolism	50–100

Modified from work by Ben-Menachem (2004), Mani and Pollard (2009), McLean (1994), Patsalos (2004), Stein and Kanner (2009), Stephen and Brodie (2012), and Vajda and Eadie (2014)

Table 2. Clinical characteristics of the most commonly used AEDs

AED	Suggested mechanism of action	Seizure type (according to SmPC)	Dose (mg)	Clinically meaningful pharmacokinetic interactions	Possible adverse effects
Carbamazepine	Blocking of Na ⁺ channels	Generalised tonic-clonic and partial seizures	800–2,000	CYP inducer – beta-blockers, dihydropyridine calcium-channel blockers, diltiazem, statins, warfarin, tricyclic antidepressants, serotonin-selective reuptake inhibitors, antipsychotics, benzodiazepines, oxycodone, omeprazole	Skin rash, nystagmus, blurred vision, ataxia, drowsiness, hyponatraemia, neutropaenia, bradycardia, heart block, weight gain, lethargy, osteoporosis
Clobazam	Activation of GABA _A receptor	Adjunctive therapy	60–80	Ethanol	Neurological and psychiatric effects, lethargy, memory problems, hyperactivity, withdrawal effects, tolerance, rebound insomnia
Gabapentin	Blocking of Na ⁺ and Ca ²⁺ channels Elevation of inhibitory transmission	Partial seizures with and without secondary generalisation	900–3,600	Morphine, aluminium, magnesium	Weight gain, leukopenia, nausea, disorientation, depression, ataxia, dizziness, skin rash, fatigue
Lamotrigine	Blocking of Na ⁺ and Ca ²⁺ channels	Partial seizures and Generalized seizures, including tonic-clonic seizures. Lennox-Gastaut syndrome.	100–200	Valproic acid, phenytoin, carbamazepine, phenobarbital, oral contraceptives, rifampicin	Ataxia, insomnia, tremor, headache, paraesthesia, nystagmus
Levetiracetam	Binding to synaptic vesicle protein 2A Elevation of inhibitory transmission Decrease in excitatory transmission	Partial onset seizures with or without secondary generalisation. Adjunctive therapy of myoclonic seizures and primary generalised tonic-clonic seizures	1,000–3,000	-	Drowsiness, headaches, ataxia, tremor, dizziness, diarrhoea, skin rash, fatigue
Oxcarbazepine	Blocking of Na ⁺ and Ca ²⁺ channels Activation of K ⁺ channels	Partial seizures with or without secondarily generalised tonic-clonic seizures	600–2,400	Immunosuppressants, oral contraceptives, carbamazepine	Hyponatraemia, disorientation, depression, somnolence, headaches, dizziness, diplopia, nausea, skin rash

Phenytoin	Blocking of Na ⁺ channels	Tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe)	200–400	CYP inducer – beta-blockers, dihydropyridine calcium-channel blockers, diltiazem, statins, warfarin, tricyclic antidepressants, serotonin-selective reuptake inhibitors, antipsychotics, benzodiazepines, omeprazole, valproic acid	Nystagmus, lack of co-ordination, hirsutism, ataxia, somnolence, mood changes, nausea, extrapyramidal abnormalities, skin rash
Pregabalin	Blocking of high-voltage-activated CA2 ⁺ channels	Adjunctive therapy with partial seizures with or without secondary generalisation	300–600	-	Disorientation, sleeplessness, dizziness, headaches, diplopia, nystagmus, nausea, muscle spasms, erection problems, weight gain
Valproic acid	Elevation of brain GABAergic activity Decreased excitatory transmission Blocking of Na ⁺ and Ca ²⁺ channels	Generalised or partial seizures	1,000–1,500	Phenytoin, carbamazepine, phenobarbitone, lamotrigine, nimodipine, amitriptyline, nortriptyline, meropenem	Gastrointestinal effects, hair loss, weight gain, polycystic ovaries, reduced sperm function

Modified from work by Asconapé (2010), Brodie and Dichter (1996), Brodie and French (2000), Kwan et al. (2001), Liu and Henry (2009), Pugh et al. (2010), Stein and Kanner (2009), Summary of product characteristics (2017), and Vajda and Eadie (2014).

2.5 OUTCOME OF AED TREATMENT

The main objective for AED treatment is to control the seizures with acceptable tolerability (Mohanraj & Brodie 2003). Most patients have an immediate response or 6–12 months' delay in response to the first AED (Stephen & Brodie 2012). About 60–85% of people developing epilepsy achieve long-term (probably permanent) remission within five years of diagnosis (Neligan et al. 2011; Shorvon & Goodridge 2013), with the likelihood being higher with newly diagnosed cases as compared to chronic epilepsy (Shorvon & Goodridge 2013). The longer it takes to reach seizure remission, the less likely is subsequent sustained remission. About 40% of patients still have active epilepsy five years after its onset (Laxer et al. 2014; Neligan et al. 2011; Noe 2011; Privitera 2011): as many as 10% enter subsequent long-term remission, 20% experience continuous epilepsy with no periods of remission, and 10% exhibit epilepsy with an intermittent pattern (Neligan et al. 2011). It has been estimated that approximately 20–30% of patients with epilepsy have more than one seizure per month (Forsgren et al. 2005).

Table 3 summarises data from several seizure-outcome studies, including patients of all ages. A population-based cohort study, the UK's National General Practice Study of Epilepsy, showed that 86% of the patients achieved three years' seizure remission and 68% five-year seizure remission (Cockerell et al. 1995; 1997; Hart et al. 1990; MacDonald et al. 2000; Sander et al. 1990), whereas the corresponding remission rates in other studies were 64% and 58%, respectively (Forsgren 1990; Lindsten et al. 2001). In hospital-based cohort studies, a one-year remission rate of 59% has been seen (Brodie et al. 2012; Hitiris et al. 2007; Kwan & Brodie 2000; 2001; Mohanraj & Brodie 2005b; 2006).

Clinical trials with newly diagnosed patients have shown that, of the various AEDs, carbamazepine displayed the best one-year remission rate, 59–76% (Heller et al. 1995), though this has also been the most commonly withdrawn AED (Heller et al. 1995; Mohanraj & Brodie 2005b). A 12-month remission was achieved more rapidly with carbamazepine than other AEDs investigated (Bonnert et al. 2012; Marson et al. 2007). Topiramate (with a hazard ratio, HR, of 1.22) showed a shorter time to treatment failure and lamotrigine less rapid failure (HR 0.78) than carbamazepine did. A study of standard and new antiepileptic drugs (SANAD) identified lamotrigine as a viable alternative to carbamazepine for focal epilepsies and confirmed valproic acid as the most effective AED for generalised epilepsy (Chadwick & Marson 2007). Lamotrigine had the best effect for focal seizures and valproic acid for generalised ones (Mohanraj & Brodie 2005b).

Patients who experience failure in their AED treatment are at increased risk of adverse health outcomes (Perucca et al. 2011); also, their mortality rate is increased (Laxer et al. 2014), especially in the first few years after diagnosis (Shorvon & Goodridge 2013). Death may be caused by the underlying cause of the epilepsy (such as a malignant brain tumour or neurodegenerative disease) or be seizure-related (as with *status epilepticus* or seizure-related accidents). Sudden unexplained death in epilepsy patients (SUDEP) is 10 times

more likely among people who continue to have generalised tonic-clonic seizures than in those who are seizure-free. In the UK's general-practice study of epilepsy, in nearly 15-year follow-up on 564 patients, there were 177 deaths (Gaitatzis et al. 2004a). In comparison to the general population of the same age and sex, the reduction in life expectancy was as great as two years for those with 'idiopathic' or 'cryptogenic' epilepsy and up to 10 years in patients with 'symptomatic' epilepsy. The deleterious effect peaked at the time of diagnosis and diminished with time.

2.5.1 Refractory epilepsy

Pharmacoresistance can be defined as a situation wherein two appropriate, well-tolerated first-line AEDs or one course of monotherapy and one combination regimen have failed because of lack of efficacy (Kwan & Brodie 2004). Estimates of the proportion of epilepsy cases that are medically resistant vary within the range 28–37% (Berg et al. 2001; Camfield & Camfield 1996; Kwan & Brodie 2000; Kwan et al. 2010); misdiagnosis and nonstandard definitions may complicate assessment of the true prevalence of medically resistant epilepsy. Refractory epilepsy can be progressive, carrying risks of structural damage developing in the brain, along with comorbidities, increased mortality, and negative psychological and social consequences.

Patients should be counselled about factors that aggravate epilepsy and on the importance of adhering to the therapy (Kwan et al. 2011). At the same time, AED treatment should be optimised and the adverse effects minimised. Resective surgery should be considered as soon as seizures are proved to be medically refractory. Also, patients with incomplete response to AEDs and who are not surgery candidates may benefit from additional medication trials or from palliative nonmedical therapies, such as neurostimulation therapies or diet therapies.

A correlation exists between the risk of seizures continuing and significant mortality/morbidity (Kwan et al. 2011; Laxer et al. 2014). Also, refractory epilepsy is associated with increased risk of nonfatal injuries (head injury, burns, and fractures) and with disability and diminished quality of life (poor academic achievement, unemployment, inability to drive, and social isolation).

2.5.2 Predictors of seizure outcome

Among the predictors of seizure outcome are the patient's early response to AEDs, the aetiology of the epilepsy, the number of seizures prior to initiation of treatment, the patient's age, EEG findings, and comorbidities (Mohanraj & Brodie 2013). In addition, early predictors of subsequent intractability have been identified: failure to respond to the first two appropriate AEDs tried, high seizure frequency prior to treatment, and certain epilepsy syndromes / seizure types and aetiologies (Laxer et al. 2014). Failure of AEDs that stems from lack of efficacy is a stronger predictor of refractoriness than is failure due to adverse effects. With each AED trial that fails, the risk of refractory epilepsy grows. Among the focal epilepsies, those associated with vascular lesions may be more responsive to treatment than those linked to hippocampal sclerosis, cortical malformations, or dual pathology. Presentation with *status epilepticus*, abnormal results of

a neurological examination, and/or developmental delay has been identified among other risk factors for refractoriness.

Table 3. Seizure outcome during antiepileptic drug treatment in patients with newly diagnosed epilepsy

Population-based cohort studies			
Study/studies	Number of patients	Age	Outcome
NGPSE (Cockerell et al. 1995; 1997; Hart et al. 1990; Macdonald et al. 2000; Sander et al. 1990)	1,008	1–90	Rate of recurrence after first attack: 67% within 12 months 78% within 36 months HR of 0.033 per week at 6 months HR of 0.007 per week at 6–12 months HR of 0.004 per week in the next 24 months Seizure-freedom: 86% for three years' remission 68% for five years' remission 84% of surviving patients in terminal remission
Goodridge and Shorvon (1983)	122	1–80	2/3 in terminal remission by 10 years 80% in terminal remission by 20 years
Forsgren (1990), Lindsten et al. (2001)	107	17–80+	Seizure-freedom: 68% one-year remission rate 64% three-year remission rate 58% five-year remission rate
Hospital-based cohort studies with newly diagnosed epilepsy patients with initial AED treatment			
Study/studies	Number of patients	Age	Outcome
Karlsson et al. (2014)	367	0–87	In the first year on the initial AED: 56% remained on the initial AED 18% switched to another AED 15% discontinued it
Brodie et al. (2012), Hitiris et al. (2007), Kwan and Brodie (2000; 2001), Mohanraj and Brodie (2005b; 2006)	1,098	9–93	Seizure-freedom: Early and sustained for 37% Delayed but sustained for 22% Fluctuation between periods of seizure freedom and relapse for 16% Never attained by 25% One-year remission for 59% Refractory epilepsy: 2× more likely if >10 pre-treatment seizures
AED trials with newly diagnosed epilepsy patients			
Study/studies	Number of patients	Age	Outcome
SANAD (Bonnett et al. 2015; Marson et al. 2007)	2,040	4–80+	Time to 12 months' remission (HR): CBZ 1, LTG 0.91, GBP 0.75, TPM 0.86, OXC 0.92 Time to treatment failure (HR): CBZ 1, LTG 0.78, GBP 1.21, TPM 1.22, OXC 1.04
Mohanraj and Brodie (2005b)	780	9–93	Seizure-freedom: Focal seizures: LTG 63%, CBZ 45%, VPA 42% Generalised seizures: LTG 45%, CBZ 31%, VPA 68% Withdrawal: LTG 7%, CBZ 16%, VPA 7%
Heller et al. (1995)	243	13–70	Seizure-freedom: One-year remission of 75% with all AEDs Withdrawal: PB 22%, PHT 3%, CBZ 11%, VPA 5%
Callaghan et al. (1985)	181	4–75	Excellent response to AED: PHT 57.1%, CBZ 33.5%, VPA 44.4%

Turnbull et al. (1985)	140	16-70	Seizure-freedom: Two-year remission: VPA 49%, PHT 56% Withdrawal: VPA 13%, PHT 23%
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NGPSE = National General Practice Study of Epilepsy

SANAD = Standard and new antiepileptic drugs

CBZ = Carbamazepine

GBP = Gabapentin

OXC = Oxcarbazepine

LTG = Lamotrigine

PB = Phenobarbital

PHT = Phenytoin

TPM = Topiramate

VPA = Valproic acid

2.6 EPILEPSY IN ELDERLY PEOPLE

2.6.1 Incidence and prevalence

Up to 0.6 million people age 65 or over have active epilepsy, and the number of new cases per year in this age group is 85,000 in Europe alone (incidence: 0.1%; prevalence: 0.7%) (Forsgren et al. 2005). On a worldwide scale, among subjects above 60 years old, the annual incidence of epilepsy is 0.1–0.13% and the prevalence is 0.9–1% (Austin & Abdulla 2013; Cloyd 2005; Faught 1999; Günter 2001; Kutluay et al. 2003; Stephen & Brodie 2000). In general, the incidence of *status epilepticus* in the elderly (0.09%) is almost two times that in adults overall (Towne 2007), and annual incidence climbs to 1.4% among people age 80 or above (Rowan 2000). Epilepsy is more common in nursing-home populations than among elderly people who live independently; the annual incidence in the former is as high as 1.6%, and the prevalence figure is 6% (Leppik 2007; 2012). In Finland, recent years have witnessed an increase in the annual incidence of epilepsy among elderly people who live outside institutions – the figure rose from 0.09% to 0.10% in men and from 0.05% to 0.06% in women between 1986 and 2002 (Sillanpää et al. 2006).

Across all age groups, approximately 30% of epilepsy cases occur in people age 65 years or above (Austin & Abdulla 2013; Cloyd 2005; Günter 2001; Kutluay et al. 2003; Stephen & Brodie 2000). It is noteworthy that the prevalence and incidence rates cited are probably underestimates, because of the difficulties in diagnosing epilepsy among the elderly. As the population gets older, epilepsy among the elderly will increase as the impact of neurodegenerative diseases grows and changes in the brain become more pronounced (Forsgren et al. 2005; Stephen & Brodie 2000).

2.6.2 Aetiology

The prevalence found for specific causes of epilepsy differs with the study population, the definitions and investigation strategies applied, and underlying pathological changes in the elderly (Brodie et al. 2009); see Figure 3. The most common aetiologies of newly diagnosed seizures in the elderly are cerebrovascular disease, neurodegenerative disease, brain tumours, and unknown factors (de Assis et al. 2015; Granger et al. 2002). The role of neurodegenerative diseases in causing epilepsy increases with age (see Figure 4).

The prevalence of cerebrovascular diseases is going to increase as the population gets older, thereby increasing the incidence of epilepsy (Van Cott 2002). The larger the haemorrhagic area, the more severe the stroke, and the closer the injury to the cortical rather than subcortical area, the more likely the patient is to suffer a seizure (Menon & Shorvon 2009; Pitkänen et al. 2015). 25–40% of the newly diagnosed cases present no identifiable aetiology for the epilepsy (Brodie & French 2000; Cloyd et al. 2005).

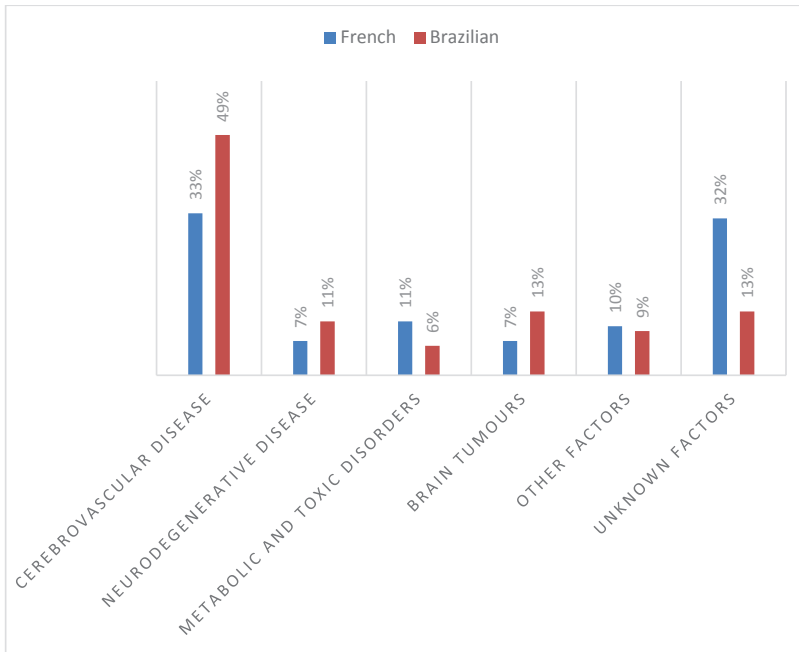


Figure 3. Aetiologies of newly diagnosed epilepsies in French ($n = 341$) (Granger et al. 2002) and Brazilian ($n = 120$) (de Assis et al. 2015) populations of people aged 60 or above ($n = 341$).

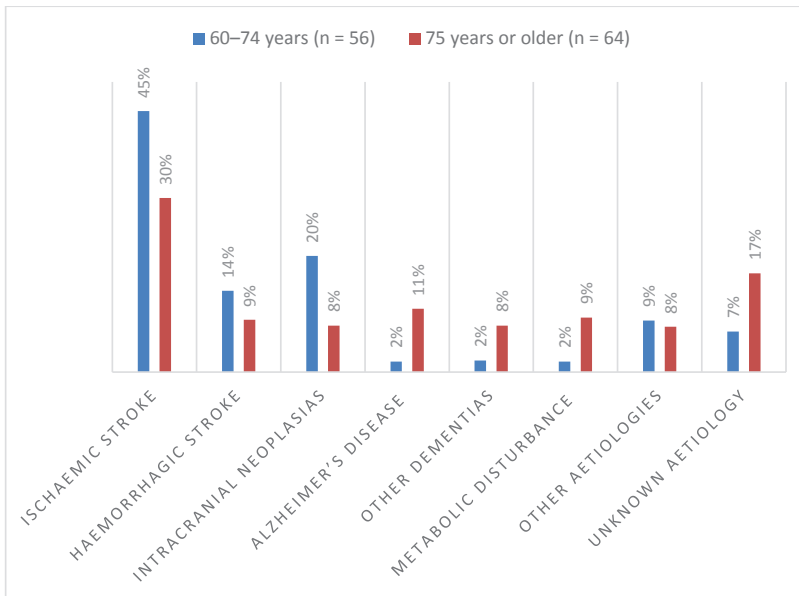


Figure 4. Comparison of epilepsy aetiologies in elderly patients 60–74 years old and those age 75 or above (de Assis et al. 2015).

2.6.3 Diagnosis

The aetiology, clinical presentation, and prognosis in cases of seizures in the elderly differ from those observed with young adults (Brodie et al. 2009; Werhahn 2009). Atypical clinical presentation of seizures create challenges in differential diagnosis; cardiovascular conditions, drug effects, infections, metabolic disturbances, sleep disorders, and psychiatric disorders can mimic epilepsy (Brodie et al. 2009; Ramsay et al. 2007; Stephen & Brodie 2008). Because seizures in the elderly may be diagnosed as memory lapses or confusion, diagnosis of epilepsy may end up delayed or wholly absent (Cloyd et al. 2005; Kirmani 2014; Lannon 1993; Pugh et al. 2009); also, physical injury during seizures and prolonged postictal confusion after them are more common among the elderly than younger adults (Brodie & French 2000). Early diagnosis of epilepsy in elderly people is important because uncontrolled seizures can lead to loss of independence, greater risk of injury, social isolation, dementia, and fear of death (Baker et al. 2001; Collins et al. 2006; Leppik et al. 2012).

When the patient has a history of injuries with physical harm (cuts or bruises) or symptoms (confusion, headaches, or drowsiness) that might be linked to seizures, a diagnosis of epilepsy may be made more readily (Collins et al. 2006; Johnston & Smith 2010; Leppik et al. 2012; Stephen & Brodie 2000). Witnessed seizures also aid in the diagnosis – others may detect initial symptoms (if any), abnormal movements, urinary incontinence, or reduced level of consciousness during a seizure.

Neuroimaging via both magnetic resonance imaging (MRI) and computed tomography (CT) is useful for patients with seizures (Collins et al. 2006; Leppik et al. 2012). In particular, MRI can reveal infarctions, neoplasms, and vascular malformations in 80% of cases. An abnormality has been found in MRI scans of 54–66% of elderly patients with epilepsy (Brodie & Stephen 2007; Stephen & Brodie 2008). In contrast, EEG is not necessarily specific in differentiating epilepsy in elderly patients: up to 12–38% of healthy patients develop EEG abnormalities, and only 10–20% of post-stroke seizures and cerebral tumours cause epileptiform EEG discharges (Liu & Henry 2009; Stephen & Brodie 2000; Van Cott 2002). Just 28% of elderly patients with epilepsy ($n = 117$ for partial and/or secondary generalised seizures) manifested changes in EEG in research by Stephen et al. (2006). Video-EEG may be helpful in selected cases (Keränen et al. 2001).

Exclusion of conditions that can mimic seizures is important (Austin & Abdulla 2013; Stephen & Brodie 2000; Werhahn 2009). In the differential diagnosis, cardiac arrhythmias, hypoglycaemia, orthostatic hypotension, carotid sinus sensitivity, and vasovagal episodes should be taken into account (Stephen & Brodie 2000), and various investigations (electrocardiographic recordings, ultrasonography, blood-pressure measurements, or haematological screening) might be needed. If the patient has a sleep disorder, polysomnography and videotelemetry are good detection tools.

2.6.4 Classification of seizures

Due to background aetiological factors of epilepsy in the elderly, most new-onset seizures in the elderly have focal onset (Brodie & French 2000; Cloyd et al. 2005; Faught 1999; Hauser et al. 1993; Stephen & Brodie 2000). Secondly generalised seizures account 25.9% of the cases in elderly patients (Ramsay et al. 1994).

2.6.5 Challenges in antiepileptic drug treatment of the elderly

AED treatment should be started as soon as a diagnosis of epilepsy and the recurrent nature of the seizures have been established (Collins et al. 2006; Leppik et al. 2012). The response to AED treatment in the elderly is usually good with low-dose monotherapy (Arryo & Kramer 2001; Collins et al. 2006; Eisenschenk & Gilmore 1999; Leppik et al. 2012). In total, 80% of the elderly patients use monotherapy and 20% use combination therapy with two or more drugs (Perucca et al. 2006b).

Elderly patients may be more vulnerable to adverse effects and interactions with AEDs than younger adults are (Austin & Abdulla 2013; Günter 2001; Stephen & Brodie 2000). Also, AED treatment can cause deterioration in physical and social functioning (Perucca et al. 2006b). Because of age-related physiological changes, tolerance of antiepileptic drugs can be poor (Cloyd 2005).

Surgery is rarely undertaken in cases of elderly patients, because the cause of the seizures seldom can be eliminated via surgery and there is an increased risk of complications (Cloyd 2005; Grivas et al. 2006).

2.6.5.1 Age-related changes in pharmacokinetics of antiepileptic drugs

In elderly patients with epilepsy, AED pharmacokinetics are altered because of metabolic and structural changes related to ageing (Bourdet et al. 2001; Jetter & Cavazos 2008; Rowan 2000). The most important change entails reduction in renal and metabolic clearance (Perucca et al. 2006b; Willmore 2000); the apparent oral clearance is reduced by, on average, 10–50% in comparison to the general adult population (Perucca 2006b). That said, predicting the effects of pharmacokinetic changes at the level of the individual is difficult, because many further factors contribute to the outcome for a specific patient with a specific AED (Perucca et al. 2006b).

In general, the absorption of drugs from the gastrointestinal tract may be decreased in older patients, while gastric emptying is delayed because of reduced motility (Leppik et al. 2012; Stephen 2003). The number of gastric parietal cells is lower, raising the ventricle pH; absorption of basic drugs is increased and that of acidic drugs decreased (neutral and weakly acidic preparations such as oxcarbazepine, lamotrigine, and valproic acid are well absorbed). The absorptive surface area and blood flow in the gastrointestinal tract are decreased.

The apparent volume of distribution for lipophilic drugs (such as carbamazepine and phenytoin) is higher because of the reduction in body mass and increase in body fat. This can cause prolongation of plasma half-life and higher drug-related toxicity (Leppik et al. 2012; Stephen 2003). Most AEDs (e.g., valproic acid, phenobarbital, and phenytoin) bind to albumin or (in the case of carbamazepine) to α_1 -acid glycoprotein. Albumin synthesis is

decreased in elderly patients, and their plasma level of albumin is about 20% lower than in 20-year-old subjects and 10% lower than in 30–40-year-olds. Levels of α_1 -acid glycoprotein rise with age in men but stay the same with women.

Decreased blood flow and enzyme activity in the liver can cause reduction in the clearance of capacity-limited drugs, such as phenytoin (Stephen 2003). The metabolism in phase-1 reactions (CYP-mediated) is reduced, but that in phase 2 (glucuronidation) is not: the metabolite is not eliminated rapidly enough, and toxicity effects can ensue. In addition, renal mass, tubular function, and renal blood flow decrease; creatinine clearance declines; and doses of some drugs (gabapentin, levetiracetam, and pregabalin) must be decreased (Italiano & Perucca 2013; Stephen 2003).

2.6.5.2 Antiepileptic drug choices in the elderly

While several sets of guidelines for the treatment of epilepsy have been published in recent years, they offer little or no guidance on the treatment of elderly patients (Glauser et al. 2013; Kälviäinen et al. 2014; Ossemann et al. 2006; Pugh et al. 2011). Treatment should be started with monotherapy and chosen individual-specifically, in line with the characteristics of each patient (Arroyo & Kramer 2001; Faught 2007). Also, the choice should consider seizure type, comorbidity, and other medications (Brodie & Stephen 2007; Garnett 2005; Groselj et al. 2005; Marasco & Ramsay 2009a; Stephen 2003). Usually, the drug doses are lower in elderly people than younger adults; accordingly, the titration of the AED dose should be slow enough and the plasma concentrations should be checked when the drug treatment is initiated (Stephen & Brodie 2000). Those AEDs that can lead to adverse cognitive and sedative effects should be avoided (Arroyo & Kramer 2001); among the drugs with a favourable profile are gabapentin, lamotrigine, oxcarbazepine, and levetiracetam (Asconapé 2002). The ideal AED for elderly patients would be effective; be taken once per day; and possess low protein-binding potential, no neurological toxicity, and no participation in drug interactions (Faught 1999).

Use of first-generation AEDs, such as phenobarbital and phenytoin, is not highly recommended for elderly patients, because of their pharmacological profile (Beghi et al. 2009; Rowan 1998; Sanya 2010), but 70% of older patients with newly or previously diagnosed epilepsy even very recently were placed on phenytoin, 10% on phenobarbital, and 10% on carbamazepine, with under 10% given gabapentin or lamotrigine (Perucca et al. 2006b). Second-generation AEDs might be more suitable than older ones because they may have less adverse effects and fewer interactions (Sabers & Gram 2000; Stephen & Brodie 2000; Willmore 2000). The last few years have seen some change in patterns of prescribing AEDs: valproic acid, lamotrigine, and levetiracetam are used more as the initial AED for the elderly, while phenobarbital, phenytoin, and carbamazepine are prescribed less (Pugh et al. 2008; 2011).

Table 4 presents clinical characteristics of the most commonly used AEDs among elderly patients. **Carbamazepine**, which does not impair psychomotor activity (Stephen & Brodie 2000), is still one of the most commonly used in elderly patients, its multiple interactions and the other problems that it might cause notwithstanding (Karlsson et al. 2014; Pugh et al. 2011). **Gabapentin** is well tolerated in the elderly: it is not metabolised,

takes part in few drug–drug interactions, has few adverse effects, and does not affect cognition (Haider et al. 1996; Rowan 2000; Stephen & Brodie 2000; Willmore 2000). Appropriate dose adjustment is important in patients with renal dysfunction (Zand et al. 2010).

Lamotrigine has good efficacy, tolerability, and a solid safety profile for elderly patients with epilepsy (Choi & Morrell 2003). It does not inhibit hepatic mono-oxygenase enzymes (Stephen & Brodie 2000), and its adverse effects on the central nervous system are largely confined to the first few weeks of treatment (Rowan 2000). Its efficacy is comparable to that of carbamazepine (Stephen & Brodie 2000). **Levetiracetam** too has a favourable safety profile in the treatment of epilepsy (Briggs & French 2004). Because it is not metabolised in the liver, it is a good choice of AED for elderly patients with hepatic diseases (Jankovic & Dostic 2012). Also, it does not interact with other drugs and is not associated with cognitive dysfunction (Kirmani et al. 2014). As adjunct therapy, it has been found safe and efficient for elderly patients (Werhahn et al. 2011). As initial AED, it has higher one-year retention and better tolerability than carbamazepine does.

Oxcarbazepine does not depend on the hepatic cytochrome P450 enzyme system for its metabolism. Hence, there are fewer clinically meaningful interactions (Kutluay et al. 2003; Stephen & Brodie 2000). Hyponatraemia is a noteworthy common side effect in patients taking oxcarbazepine, especially when the drug is used concomitantly with diuretics (Kim et al. 2014).

Studies in the United States have shown **phenytoin** to be, until only recently, the most commonly prescribed initial AED for elderly patients, although it has a narrow therapeutic range, many potential interactions with other drugs, and numerous adverse effects (Hope et al. 2009; Leppik & Birnbaum 2009; Pugh et al. 2011; Rowan 2000; Ruggles et al. 2001). Speaking in its favour is that it does not impair cognitive function (Stephen & Brodie 2000). **Pregabalin** is more potent than gabapentin and absorbed more predictably (Leppik & Birnbaum 2009), but, on account of sparseness of clinical data, it remains largely confined to adjunctive therapy for epilepsy (Brodie 2004; Leppik & Birnbaum 2009). **Valproic acid** has been used in elderly patients for 35+ years. It is quite well tolerated (Stephen 2003; Stephen & Brodie 2000) and represents a useful option for the elderly population, but it is not necessarily the best first-line treatment for focal epilepsy (Perucca et al. 2006a).

Phenobarbital has been used in elderly patients either on its own or in combination with phenytoin, but in recent years its use has decreased because of its sedative quality, adverse behavioural effects, and interactions with other drugs (Stephen & Brodie 2000). Use of **clobazam** as monotherapy for epilepsy is rare; there is no good evidence of its advantages over carbamazepine, and the data point to only a slight advantage over phenytoin with respect to retention (Arya et al. 2014). Finally, **topiramate** has predictable pharmacokinetics and minimal protein binding, so, it has possibilities as a choice of AED for elderly patients (Groselj et al. 2005).

Table 4. Clinical characteristics of the most commonly prescribed antiepileptic drugs in elderly patients with epilepsy

AED	Daily dose (mg)	Times/ day	Age-related changes in pharmacokinetics	Adverse effects common with old age	Possible age-related problems
Carbamazepine	100–800	1–2	Protein binding decreased	Rash, nausea, headaches, dizziness, diplopia, ataxia, osteomalacia, osteoporosis	Induced metabolism of other lipid-soluble drugs; interactions with concomitant drugs. Reduction in serum protein levels: increase in free fraction (can lead to toxicity). Cognitive effects.
Gabapentin	900	3	-	Somnolence, dizziness, ataxia, fatigue, weight gain	Neurotoxicity with high doses.
Lamotrigine	300	2	-	Dizziness, asthenia, somnolence, headaches, rash, Stevens–Johnson syndrome	High discontinuation rate, on account of skin rashes.
Levetiracetam	1,000	2	-	Somnolence, dizziness, asthenia, headaches	Aggression and mood lability as the most common reasons for discontinuation. Confusion and slowing of mental function as possible problems.
Oxcarbazepine	600–1,200	2	-	Drowsiness, dizziness, headaches, nausea, vomiting, ataxia, hyponatraemia	Reduction in serum protein levels: increase in free fraction (can lead to toxicity). Hyponatraemia as an adverse effect (sodium levels should be checked regularly)
Phenytoin	200	1	Protein binding decreased with reduced serum albumin levels and in renal failure	Osteoporosis, osteomalacia, ataxia, rash, hepatotoxicity	Saturation kinetics: slowing of elimination with higher doses (can lead to toxicity). Many interactions with other drugs. Reduction in serum protein levels: increase in free fraction (can lead to toxicity).
Pregabalin	600	2	-	Dizziness, ataxia, nausea, drowsiness, weight gain, oedema	Lack of clinical data on efficacy and tolerability.
Valproic acid	750	3	Protein binding decreased	Tremor, encephalopathy, weight gain	Decrease protein binding and age-related reduction in serum protein levels: increase in free fraction (can lead to toxicity). Action as a metabolic inhibitor: interactions with other AEDs (increase in plasma concentrations). Need for higher doses when used with hepatic-enzyme-inducing drugs.

Modified from work by Gareri et al. (1999), Kirmani et al. (2014), Leppik and Birnbaum (2009), Stephen (2003), Stephen and Brodie (2000), and Willmore (2000)

2.6.5.3 Efficacy and safety of antiepileptic drugs as initial treatment

Most of the evidence as to the efficacy and safety of AEDs come from studies of populations below 65 years of age, and there have been few randomised clinical trials with elderly patients (Brodie et al. 1999; Rowan et al. 2005; Saetre et al. 2007; Werhahn et al. 2015). The AEDs studied most frequently in elderly patients with focal epilepsy are carbamazepine, lamotrigine, gabapentin, topiramate, and valproic acid. These drugs have showed a proven effect as initial monotherapy in older patients with newly diagnosed seizures (Glauser et al. 2013).

Table 5 summarises the results available from randomised clinical trials of AEDs with elderly patients. **Carbamazepine** is the AED that has been investigated best with respect to older patients. It has shown good efficacy in comparison with other AEDs, but second-generation AEDs have been found to be better tolerated (Brodie et al. 1999; Rowan et al. 2005; Saetre et al. 2007; Werhahn et al. 2015). **Gabapentin** showed efficacy levels similar to those of lamotrigine and carbamazepine while being better tolerated than carbamazepine (Rowan et al. 2005). **Lamotrigine**, in turn, has demonstrated its efficacy and safety as initial AED for elderly patients (Brodie et al. 1999; Rowan et al. 2005; Saetre et al. 2007; Werhahn et al. 2015); it was more effective than carbamazepine (Brodie et al. 1999) and better tolerated than carbamazepine and gabapentin (Brodie et al. 1999; Rowan et al. 2005). **Levetiracetam** showed efficacy comparable to that of carbamazepine and lamotrigine but was better tolerated than those two AEDs (Werhahn et al. 2015).

There have been few clinical trials with **oxcarbazepine** in the context of elderly patients, and no data from randomised comparative trials are available (Dogan et al. 2008), though this drug is known to have less adverse events in elderly patients than younger ones (Kutluay et al. 2003). Although **phenytoin** is still the AED prescribed most often for treatment of elderly patients with epilepsy (Hope et al. 2009; Leppik & Birnbaum 2009; Pugh et al. 2011; Rowan 2000; Ruggles et al. 2001), good clinical data attesting to its effectiveness and safety with elderly people remain absent. While **valproic acid** has been the subject of many studies, those focusing on elderly patients remain in the minority (Stephen 2003). These studies show that it has the same effect as carbamazepine, phenytoin, and phenobarbital on focal-onset and general-onset tonic-clonic seizures. The adverse events were the same for elderly and for younger adults and consisted mainly of gastrointestinal symptoms: nausea, vomiting, heartburn, and abdominal pain.

Table 5. The efficacy and safety shown in various studies of antiepileptic drugs in elderly patients with newly diagnosed epilepsy

Randomised controlled trials						
Reference	AED treatment	Number of patients	Age	Study design	Effectiveness	Safety
Werhahn et al. (2015)	CBZ, LEV, LTG	359	60–95	52-week randomised double-blind study	Seizure-freedom: No difference between groups	Retention rate: LEV 61.5%, CBZ 45.8%, LTG 55.6% Withdrawal: CBZ 32.2%, LEV 17.2%, LTG 26.3%
Saetre et al. (2007)	LTG, CBZ	185	65–91	40-week randomised multi-centre double-blind study	Seizure-freedom (in the last 20 weeks): LTG 52%, CBZ 57%	Completion of study: LTG 73%, CBZ 67% Withdrawal: LTG 14%, CBZ 25%
Rowan et al. (2005)	LTG, GBP, CBZ	593	≥65 years (scale not available)	12-month randomised study	Mean seizure-freedom: 63.2% at three months 58.6% at six months 54.4% at 12 months	Withdrawal: LTG 12.1%, GBP 21.6%, CBZ 31%
Brodie et al. (1999)	LTG, CBZ	150	65–94	24-week randomised trial	Seizure-freedom: LTG 39%, CBZ 21%	Withdrawal: LTG 29%, CBZ 58% Withdrawal due to adverse events: LTG 18%, CBZ 42%

CBZ = Carbamazepine
 GBP = Gabapentin
 LEV = Levetiracetam
 LTG = Lamotrigine

2.6.6 Seizure outcome

There is a paucity of good clinical data on seizure outcome in the elderly-patients group (Besocke et al. 2013; Brodie & Stephen 2007; Phabphal et al. 2013; Stephen et al. 2006). Table 6 summarises what is known. Complete seizure control has been estimated to occur in 70% of these patients (Brodie & French 2000). The prognosis with AED treatment after at least 12 months of treatment is good, with approximately 80% of the patients achieving seizure-freedom of at least 12 months via one or two drugs as monotherapy (Besocke et al. 2013; Stephen et al. 2006). With initial-AED treatment, the frequency of seizure-freedom among the patients was 64–77% at the first year (Besocke et al. 2013; Brodie & Stephen 2007; Stephen et al. 2006) and 57–57% at year 2 (Besocke et al. 2013; Phabphal et al. 2013). The percentage of seizure-free patients stays quite high in later months also (e.g., about 70% at 30 months) (Besocke et al. 2013).

The data available show that the rate of response to AEDs and the frequency of seizure-freedom tend to be higher in the elderly than in younger adults (Arain & Abou-Khalil 2009; Beghi et al. 2009; Brodie & Stephen 2007; Faught 1999). Response is usually achieved with AED monotherapy (Arain & Abou-Khalil 2009). Uncontrolled epilepsy is associated with excess mortality, cognitive and behavioural dysfunction, social disadvantages, increased risk of adverse AED effects, psychiatric comorbidities, physical injury, and death (Choi et al. 2008; Tomson et al. 2008).

Table 6. Data from various outcome studies considering elderly patients

Seizure outcome with initial antiepileptic drug treatment in cases of newly diagnosed epilepsy						
Reference(s)	Number of patients	Age	Study design	Follow-up period	Seizure-freedom	Other results
Besocke et al. (2013)	122	72-83 (IQ-SQ)	Retrospective study with cohorts from multiple institutions	15 months (median)	90% at six months 77% at 12 months 74% at 18 months 67% at 24 months	Adverse effects in 30% ILAE classification proposal for drug-resistant epilepsy: 55.8% seizure-free, 12.3% treatment failure, 32% undetermined seizure outcome
Phabphal et al. (2013)	278	73.32 ±8.72	Retrospective hospital-based case-controlled study	Two years	57% for ≥2 years	Seizure recurrence in ≥2 years: 43% As the most common comorbidities, depression, anxiety, sleep-related disorders, stroke (no differences between seizure-free and seizure-recurrence patients)
Brodie and Stephen (2007), Stephen et al. (2006)	117	65-92	Prospective study from the Epilepsy Unit at Glasgow's Western Infirmary	20-year period	64% with initial AED for ≥1 year (84% with pharmacological manipulation: 93% with monotherapy and 7% with duotherapy)	Uncontrolled epilepsy for 23% Withdrawal in 12% No difference in response between individual AEDs

2.6.7 Comorbidity in cases of epilepsy

Comorbid conditions are more commonplace among patients with epilepsy than those without epilepsy (Elliott et al. 2008; 2009; Gaitatzis et al. 2012; Trinka 2003). Prevalence ratios for common neurological and medical conditions in people with epilepsy are approximately 2–7 times higher than the corresponding figures for the general population (Gaitatzis et al. 2004b; Téllez-Zenteno et al. 2005), and the risk is greater for strokes (Li et al. 1997), migraines (Ottman & Lipton 1994), dementia (Hesdorffer et al. 1996a), brain tumours (Forsgren & Nyström 1990) and other neoplasms (Lamminpää et al. 2002; Nuyen et al. 2006), cardiovascular disorders (Li et al. 1997), anaemia (Nuyen et al. 2006), fractures, and decreased bone-mineral density (Annegers et al. 1989; Vestergaard 2005).

In adults with epilepsy, the most common comorbid conditions are chronic pulmonary disease, hypertension, cerebrovascular disease, receiving fractures, depression, and alcohol abuse (Germaine-Smith et al. 2011). In a multivariable logistic regression analysis, patients with cerebrovascular disease, dementia, a brain tumour, head injuries, or other central nervous system conditions were found to be more likely to experience new-onset epilepsy (Pugh et al. 2009). In contrast, a statin prescription, more advanced age, obesity, and hypercholesterolaemia were associated with a lower risk of epilepsy.

Cognitive deficiencies are more common in patients with epilepsy (Carreno et al. 2008; Hirsch et al. 2003; Motamedi & Meador 2003), especially elderly ones (Hirsch et al. 2003; Miller et al. 2016), and are influenced by the type and location of the epileptogenic lesion, the epileptic syndrome, seizure type, and the age of onset (Carreno et al. 2008). Early diagnosis and prompt initiation of AED treatment is important for preventing cognitive impairment, yet, while AEDs can prevent cognitive impairment by stopping the seizures, they can have undesirable effects on cognition and behaviour (Motamedi & Meador 2003), and polytherapy can increase the risk of impairment in some cognitive domains (Carreno et al. 2008; Miller et al. 2016), such as language skills (Miller et al. 2016). The most significant cognitive impairments are linked to focal epilepsy (Carreno et al. 2008).

2.6.7.1 The mechanism of relationship between epilepsy and comorbid conditions

The relationship between epilepsy and comorbid conditions can be explained in most cases by a causal or resultant effect (Gaitatzis et al. 2012) (see Figure 5). **Causal** comorbidity results in the development of epilepsy: stroke, brain tumours (Gaitatzis et al. 2012), and migraines (Bigal et al. 2003) can have a direct causal relationship with epilepsy. Indirect causality occurs with some conditions, such as hypertension, heart failure, and diabetes mellitus (Hesdorffer et al. 1996b; Ng et al. 1993; Wills & Hovell 1996) – direct risk factors for conditions that lead to epilepsy (Gaitatzis et al. 2012).

Resultant comorbidities arise from AED treatment (in cases of allergic reactions or osteoporosis) or because of repeated seizures (in cases of fractures or headaches) (Coppola et al. 2009; Kwan et al. 2008; Lado et al. 2008; Schon & Blau 1987; Tomson et al. 2004; Zaccara et al. 2007). Some conditions (dementia, migraines, etc.) can precede or follow the development of epilepsy (Bigal et al. 2003; Breteler et al. 1991; 1995; Hesdorffer et al. 1996a).

Shared risk factors (environmental, biological, structural, and genetic factors) create a predisposition to the development of two independent conditions: epilepsy and a specific comorbid disease (Gaitatzis et al. 2012). With some conditions, such as bowel disorders, thyroid conditions, and asthma, the mechanism of association with epilepsy remains **uncertain**.

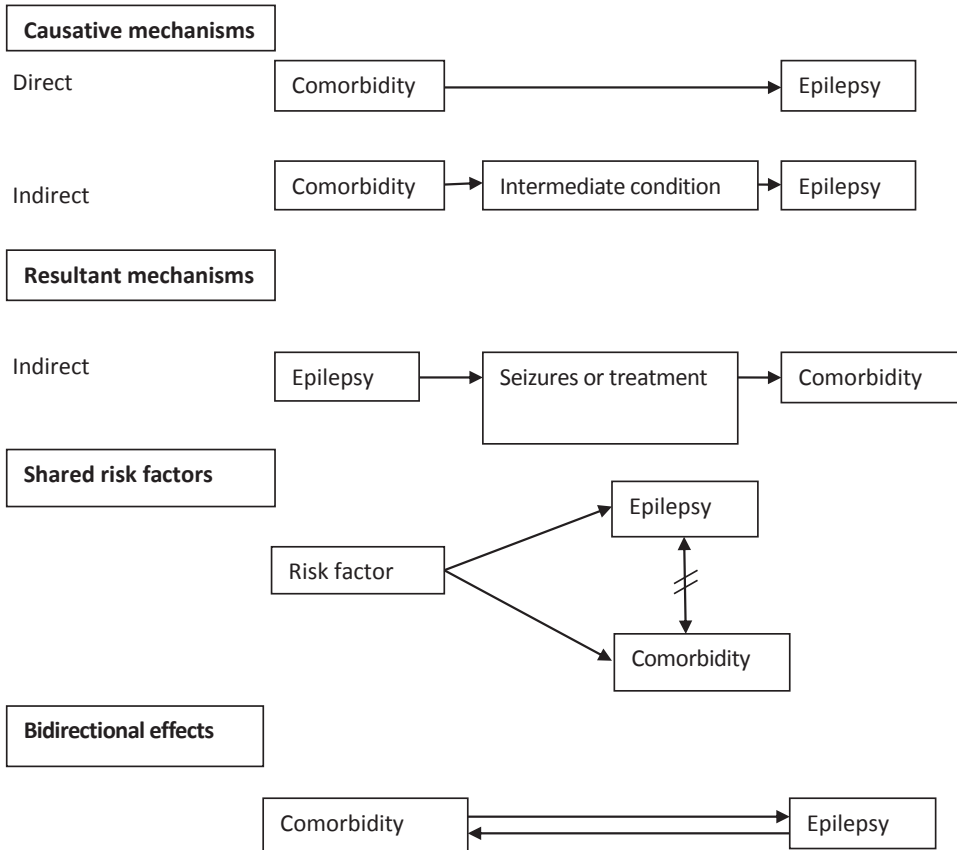


Figure 5. Mechanisms of association between epilepsy and its comorbidities. Figure modified from work by Keezer et al. (2016).

2.6.7.2 Elderly patients with comorbid conditions

In elderly patients, newly diagnosed epilepsy is associated with comorbid illnesses more often than not (Perucca et al. 2006b). These patients exhibit comorbid conditions (such as cerebrovascular disease, dementia, cardiovascular disease, and psychiatric illnesses) significantly more often than do elderly people without epilepsy (Perucca et al. 2006b; Pugh et al. 2004); see Figure 6. Cerebrovascular disease, hypertension, heart disease, diabetes mellitus, renal disease, and dementia are all related to epilepsy – they can contribute to the causation and consequences of seizures and can impair the effectiveness of treatment (Rowan 2005). Asthma, migraines, and brain tumours occur more often in younger adults (people of ≤ 64 years), while cardiovascular diseases, strokes, dementia, and meningiomas are seen more often in older patients (i.e., those >64 years old) (Gaitatzis et al. 2004b).

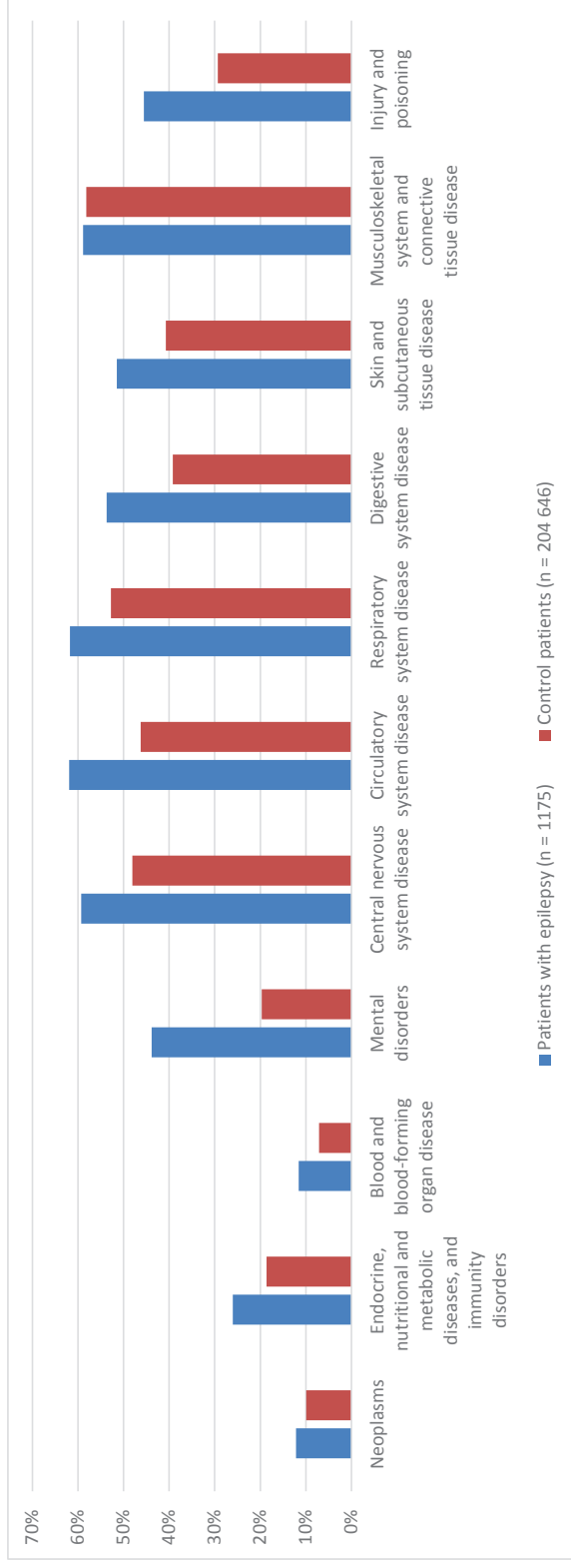


Figure 6. Prevalence of comorbid conditions in patients with epilepsy and in control patients aged 64 years or above (Gaitatzis et al. 2004b).

Many patients with epilepsy have one or more coexisting medical conditions (Gaitatzis et al. 2002; 2004b). Comorbidities increase the challenges involved in managing the epilepsy. For instance, multiple organ failure can lower the seizure threshold and affect AED metabolism (Boggs 2001). Also, AED toxicity can be influenced by a comorbid condition, and clinically relevant drug–drug interactions are possible between AEDs and drugs used to treat comorbid conditions (Zaccara 2009).

2.6.7.3 Specific conditions that are comorbid with epilepsy

A history of strokes or the presence of risk factors for stroke is associated with increased lifetime risk of epilepsy (Boggs 2001; Pitkänen et al. 2015). **Cerebrovascular disease** is the most commonly identified reason for epilepsy in the elderly patients (Ramsay et al. 2004). In these cases, epilepsy usually develops within months or years after a cerebrovascular accident (De Reuck et al. 2008). Among all elderly people, 40% of newly diagnosed epilepsy patients, 17% of people diagnosed with epilepsy earlier, and 5% of otherwise healthy people have cerebrovascular diseases (Perucca et al. 2006b). Seizure-freedom with monotherapy is more often achieved in patients whose epilepsy has cerebrovascular causes as compared with other symptomatic / 'cryptogenic' case (Zaccara 2009). **Cardiovascular diseases** are more common among elderly patients with epilepsy than in the elderly population at large (Shmueli et al. 2016). A study by Ramsay and colleagues (2004) shows that most elderly people with newly diagnosed epilepsy display risk factors for cardiovascular disorders such as dyslipidaemia (80%), hypertension (65.9%), and diabetes (28%). Carbamazepine can influence cardiac function, affecting atrioventricular conduction (Stefan 2011).

Approximately 6% of new epilepsy cases in younger adults and 10% in the elderly (65 years or above) are associated with **neurodegenerative** disorders (Friedman et al. 2012). Dementia is an important risk factor for seizures (Jenssen & Schere 2010): of all elderly people, 21% with newly diagnosed epilepsy, 17% of those previously diagnosed with it, and 5% of otherwise healthy patients have dementia (Perucca et al. 2006b). Approximately 10–22% of patients with Alzheimer's disease suffer at least one unprovoked seizure (Mendez & Lim 2003), usually occurring in the later stages of progression of the disease (Mendez et al. 1994), or earlier in cases of early-onset familial Alzheimer's (Janssen et al. 2000). Epilepsy combined with dementia has significant consequences for the prognosis with regard to the dementia: the patient's cognitive performance and autonomy can worsen, risk of injury increases, and the mortality rate rises (Hommet et al. 2008). The AED treatment should commence as soon as the diagnosis of epilepsy is certain, and it should employ a drug with minimal adverse cognitive effects – second-generation AEDs have advantages over first-generation ones for this patient group (Hommet et al. 2008; Mendez & Lim 2003). The frequency of seizures is usually low and the response to AED treatment good (Friedman et al. 2012). Non-vascular dementia in patients with seizures is easier to control than vascular dementia (Van Cott 2002).

Psychiatric comorbidities may be present in patients with epilepsy (Cloyd 2005; Hermann et al. 2000). The prevalence both of depression and of epilepsy increases with age. Depression and anxiety disorders are the most common psychiatric illnesses in elderly people with epilepsy (Gilliam et al. 2003). Depression in patients with epilepsy can cause social and vocational disability, and it can lead to learned helplessness, limbic system dysfunction, and susceptibility to the latter. Cases involving both epilepsy and depression

involve a considerably greater negative impact on socio-economic situation than either condition on its own. Also, depression and anxiety in epilepsy cases are associated with a poor outcome, and a history of depression and attempted suicide increases the risk of seizures. Finally, psychiatric comorbidities may be associated with treatment-resistant epilepsy (Hitiris et al. 2007).

Epileptic seizures double the risk of fractures and increase the likelihood of falls and impaired bone health (Cloyd 2005; Ensrud et al. 2004). Some antiepileptic drugs (e.g., phenytoin, phenobarbital, and valproic acid) decrease bone density and cause **osteoporosis** in 15–40% of patients, with the mechanism lying in interference with sex steroid and vitamin D metabolism through induction of cytochrome P450 enzymes or by direct effect on bone matter (Bergey 2004; Sheth 2002; Stefan 2011). The risk of fractures shows a significant increase with the cumulative duration of AED treatment (Kirmani et al. 2014).

A wide range of **autoimmune and inflammatory disorders** can be linked with epilepsy (Verrotti et al. 2012; Vincent & Crino 2011). Antibodies against glutamic acid decarboxylase (GAD) can be associated with type 1 diabetes mellitus and with many neurological disorders, epilepsy among them, although the pathogenic mechanism of development of epilepsy is yet unknown. Metabolic conditions (hypoglycaemia and hyperglycaemia) connected with diabetes may have an effect on development of seizures. Epilepsy can complicate multiple sclerosis (MS) and systemic lupus erythematosus (SLE) and may appear alongside them, but the mechanism is still unknown (Vincent & Crino 2011). There is a known association between thyroid disorders and encephalopathies (Hashimoto's encephalopathy in particular); seizures can be caused by many mechanisms, including ischaemia, neuronal damage, and immune-system response.

Among patients with newly diagnosed epilepsy, a cerebral **tumour** is the cause in 4% of cases (Olafsson et al. 2005). Patients with cancer are at increased risk of developing seizures: about 20% of systemic cancers may metastasise to the brain (Weller et al. 2012). Patients with metastases or with primary brain tumours have a 20–80% risk of developing epilepsy. Anti-neoplastic agents, cranial irradiation, and complications of surgery can lower the threshold to seizures (Boggs 2001), and chemotherapy agents used in combination with AEDs have toxic effects (Singh et al. 2007; Van Breeman et al. 2007). Treatment is challenging because brain-tumour-related epilepsies are usually drug-resistant (Maschio & Dinapoli 2012). While prophylactic use of AEDs in patients who do not suffer any seizures is discouraged, patients with chronic, repeated seizures need long-term AED treatment (Bauer et al. 2014).

2.6.7.4 Prognosis in cases of epilepsy with comorbid conditions

Comorbidities with epilepsy are associated with poor health outcomes: more health care is needed, quality of life is decreased, and mortality is higher (Gijssen et al. 2001). Two thirds of premature deaths can be attributed to coexisting conditions in patients with epilepsy (Gaitatzis & Sander 2004). Somatic conditions can lower the seizure threshold and can alter the metabolism and excretion of AEDs (Gaitatzis et al. 2012). In addition, long-term AED treatment can lead to development or worsening of somatic conditions.

Somatic comorbidity has been shown to have a negative impact on quality of life in adults with epilepsy (Elliott et al. 2009; Liou et al. 2005; Pugh et al. 2006), and the effect is more pronounced in older patients, with multiple chronic conditions causing a more rapid

decline in physical and cognitive functioning (Caughey et al. 2010; Comijs et al. 2009; Kriegsman et al. 2004). In patients at least 65 years old with new-onset epilepsy, the risk of medical admission is five times that among those without epilepsy; the most significant factors are myocardial infarction, gallbladder disease, anaemia, angina, and dependence on alcohol (Copeland et al. 2011).

People with somatic epilepsy that has a known cause are less likely to achieve seizure-freedom when compared to those with idiopathic epilepsy (Semah et al. 1998). Patients who have focal epilepsy that is due to ischaemic stroke, primary tumour, or cortical dysplasia achieve at least one year's seizure-freedom in 67%, 63%, and 54% of cases, respectively (Stephen et al. 2001).

2.6.8 Potential interactions with antiepileptic drugs

Management of epilepsy in the elderly is rendered challenging by numerous comorbid conditions and potential pharmacokinetic drug–drug interactions between AEDs and other medication, as presented in Figure 7 (Anderson 2004; Beghi et al. 2009; Jetter & Cavazos 2008; Lackner et al. 1998; Levy & Collins 2007; Mani & Pollard 2009; Marasco & Ramsay 2009b; Pugh et al. 2010; Werhahn 2009). Pugh and colleagues (2010) identified potential drug–drug interactions involving antiepileptic drugs (AED-PDI) in 45.5% of the elderly patients exposed to the AEDs. Relative to younger adults, elderly patients with epilepsy are susceptible to more drug interactions at lower serum AED concentrations (Perucca et al. 2006b).

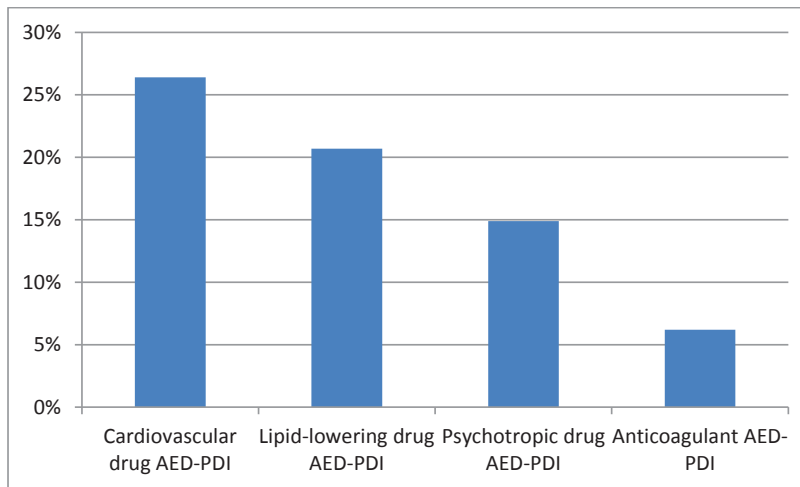


Figure 7. Potential drug–drug interactions involving antiepileptic drugs ('AED-PDI') among veterans of age 66 and above with new diagnosed epilepsy ($n = 9,682$) (Pugh et al. 2010).

AEDs may display pharmacokinetic and pharmacodynamic interactions with other drugs (Mani & Pollard 2009), but there is great heterogeneity in the extent of the interactions, because of genetic and environmental influences on drug metabolism. Pharmacodynamic interactions are not as well characterised as pharmacokinetic interactions are (Perucca 2006a), with efficacy and tolerability proving difficult to document objectively (Zaccara & Perucca 2014).

The AEDs most often involved in interactions are the **first-generation AEDs** (phenytoin, carbamazepine, phenobarbital, and primidone) (Mani & Pollard 2009; Patsalos & Perucca 2003; Perucca 2006a; Pugh et al. 2010; Schmidt & Schachter 2014); see Table 7. They induce many CYP and glucuronyl transferase enzymes, and reduction in the plasma concentration of many psychotropic, immunosuppressant, anti-neoplastic, anti-microbial, and cardiovascular agents is possible (Mani & Pollard 2009; Patsalos & Perucca 2003; Perucca 2006a; Pugh et al. 2010). This can lead to loss of therapeutic efficacy unless the dosage is increased to compensate (Patsalos et al. 2002). Also, toxic reactions are possible through interaction of AEDs with other drugs (Mani & Pollard 2009; Patsalos & Perucca 2003; Perucca et al. 2006b). For instance, although valproic acid does not induce the metabolism of hepatic enzymes in the elderly, it can cause clinically relevant interactions by inhibiting

the metabolising of other drugs (Perucca 2006a): elevation of amitriptyline and nortriptyline levels is possible, creating potential for toxicity (Stephen 2003).

In general, **second-generation AEDs** do not have many clinically important enzyme-inducing effects, though they may be a target of metabolically mediated drug interactions (Perucca 2006a; Stephen 2003). Oxcarbazepine and lamotrigine may stimulate the metabolism of oral contraceptives (Perucca 2006a). Levetiracetam, gabapentin, and pregabalin have not been reported to cause clinically meaningful interactions (Levy & Collins 2007; Perucca 2006a) (see Table 7).

Table 7. AED metabolism and interactions

AED	Enzyme-inhibiting potential	Enzyme-inducing potential	Interaction of AEDs with other drugs
Carbamazepine	-	+++	Acts as a broad-spectrum inducer
Gabapentin	-	-	Shows no interactions
Lamotrigine	-	+	Induces UGTs
Levetiracetam	-	-	Shows no interactions
Oxcarbazepine	+	-	Induces CYP3A4 and UGTs, inhibits CYP2C19
Phenytoin	-	+++	Acts as a broad-spectrum inducer
Pregabalin	-	-	Shows no interactions
Topiramate	+	+	Induces CYP3A4, inhibits CYP2C19
Valproic acid	+++	-	Acts as a broad-spectrum inducer

UGTs = UDP-glucuronosyltransferases

Modified from work by Mani and Pollard (2009) and by Perucca (2006a)

Table 8, below, sums up the most important clinically relevant interactions between AEDs and other drugs. The AEDs accelerate metabolism of lipophilic beta-blockers (propranolol, metoprolol, and timolol), while hydrophilic beta-blockers (sotalol and atenolol) do not interact with AEDs (Perucca et al. 2006b). Calcium-channel blockers (diltiazem and verapamil) are CYP3A4 inhibitors and increase carbamazepine and phenytoin concentrations (Levy & Collins 2007; Perucca et al. 2006b). Other antihypertensives (e.g., angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, and thiazide diuretics) have less potential for metabolic drug interactions (Levy & Collins 2007). HMG-CoA reductase inhibitors (atorvastatin, lovastatin, fluvastatin, and simvastatin) are metabolised through CYP3A4 and glucuronidation; carbamazepine and phenytoin may decrease their effect (Perucca et al. 2006b). Warfarin is metabolised via CYP2C9 and CYP3A4 enzymes, which can lead to interactions with first-generation AEDs but not second-generation AEDs, such as oxcarbazepine (Levy & Collins 2007 Perucca et al. 2006b).

Antidepressants, which are commonly used for the elderly, are usually not highly sensitive to antiepileptic drugs (Perucca et al. 2006b); citalopram, escitalopram, venlafaxine, duloxetine, and mirtazapine show the least potential for metabolic AED interactions (Levy & Collins 2007; Perucca et al. 2006b), though some interactions may occur – e.g., fluoxetine inhibits many cytochrome P450 isoforms and thereby inhibits metabolism of first-generation AEDs (Perucca et al. 2006b) (see Table 8). Finally, treatment of Alzheimer's disease can be difficult because of possible interactions, though the potential for these metabolic interactions is quite low (Levy & Collins 2007; Perucca et al. 2006b).

Table 8. The most important clinically meaningful potential interactions between AEDs and other drugs

Drug group	Specific drug	Pharmacological outcome of drug interaction	AED
Cardiovascular drugs			
Antiarrhythmics	Amiodarone	Increased plasma concentration of PHT	PHT
	Digoxin	Decreased concentration of digoxin	CBZ, PHT, PB, TPM
Beta-blockers	Diltiazem	Increased level of the AED	CBZ, PHT
	Propranolol, metoprolol, timolol	Decreased level of the beta-blocker	CBZ, PHT, PB
Dihydropyridine calcium-channel blockers	Amlodipine, nimodipine, nilvadipine, nisoldipine, felodipine	Decreased effect of the calcium-channel blocker	CBZ, PHT, PB
	Verapamil	CBZ toxicity	CBZ
	Nimodipine	50% increased plasma concentration of nimodipine	VPA
HMG-CoA reductase inhibitors (statins)	Atorvastatin, lovastatin, fluvastatin, simvastatin	Increased clearance, with a decreased effect of statins	CBZ, PHT, PB
		Inhibited metabolism of statins	VPA
Haematological agents			
	Warfarin	Reduced plasma level and decreased anticoagulant effect of warfarin, with a decrease in prothrombin time	CBZ, PHT
		Increased warfarin concentration	VPA
		Increased warfarin action	PHT
	Abixaban, rivaroxaban, dabigatran	Decreased anticoagulant concentration	CBZ, PHT
Central nervous system agents			
Tricyclic antidepressants	Amitriptyline	Reduced plasma concentrations of amitriptyline	CBZ, VPA
	Nortriptyline, clomipramine, amitriptyline	PHT toxicity	PHT
	Nortriptyline, clomipramine	Inhibited metabolism of antidepressants	VPA
	Amitriptyline, clomipramide, nortriptyline, desipramine, desmethyl-clomipramine, imipramine, doxepin, protriptyline	Decreased concentration of antidepressants	CBZ, PHT
Serotonin-selective reuptake inhibitors (SSRIs)	Fluoxetine	Inhibited metabolism of the AED	CBZ, PHT, PB
	Paroxetine	Inhibited metabolism of paroxetine	VPA
	Sertraline	Increased concentration of the AED	PHT, VPA, LTG
	Citalopram, paroxetine	Decreased concentration of the SSRI	CBZ, PHT
	Paroxetine	Reduced plasma concentrations of the SSRI	PHT, PB
Other antidepressants	Bupropion, mianserin, mirtazepine	Decreased concentration of the antidepressants	CBZ, PHT
	Bupropion	Reduced plasma concentrations of the antidepressant	PB
Antipsychotics	Haloperidol, chlorpromazine, clozapine, olanzapine, risperidone, quetiapine, ziprasidone	Reduced serum levels of the antipsychotics	CBZ, PHT

Benzodiazepines	Alprazolam, clobazam, clonazepam, desmethyldiazepam, diazepam, midazolam	Decreases concentration of benzodiazepines	CBZ, PHT, PB
Opioids	Oxycodone	Decreased concentration of oxycodone	CBZ, PHT, PB
Cholinesterase inhibitors	Donepezil, galantamine	Reduced levels of cholinesterase inhibitors	CBZ, PHT, PB
N-methyl-D-aspartate receptor antagonist	Memantine	Memantine being eliminated without being metabolised	CBZ, PHT, PB
Gastrointestinal drugs			
Proton-pump inhibitors	Omeprazole	Increased plasma concentration of the AED (toxicity)	CBZ, PHT, OXC
		Increased serum concentration of the AED	CLB
Other drugs	Cimetidine	AED toxicity	CBZ, PHT, PB
	Sucralfate	Decreased effect of the AED	PHT
Oral contraceptives		Increased risk of contraceptive failure	CBZ, PHT, PB, OXC

CBZ = Carbamazepine

CLB = Clobazam

OXC = Oxcarbazepine

PB = Phenobarbital

PHT = Phenytoin

TPM = Topiramate

VPA = Valproic acid

Modified from work by Levy and Collins (2007), Mani and Pollard (2009), Patsalos and Perucca (2003), Patsalos et al. (2002), Perucca (2005), Pugh et al. (2010), and Zaccara and Perucca (2014)

3 Aims for the Study

Treating elderly patients by means of antiepileptic drugs is challenging on account of the paucity of knowledge as to the AEDs' efficacy, safety, and pharmacokinetics in this population. Furthermore, comorbidity and therapy for other conditions may increase the problems that arise in AED-based treatment. Therefore, the aim of the study was to examine the choice of AED, outcome, and interactions with AEDs in the treatment of patients age 65 years or above with newly diagnosed epilepsy, where epilepsy patients of ages 16–64 years served as a control group.

More specifically, the aims were to assess the following:

1. The choice of first AED in community-dwelling elderly patients with newly diagnosed epilepsy in Finland
2. The outcome of initial AED monotherapy among elderly patients with newly diagnosed epilepsy and the cumulative probabilities of ≥ 2 - and ≥ 5 -year complete seizure remission
3. Potential pharmacokinetic drug–drug interactions and comorbid conditions associated with epilepsy in the elderly patients with recent-onset epilepsy

4 Materials and methods

4.1 PATIENTS

To identify community-dwelling elderly patients with newly diagnosed epilepsy, we used two data sources: the case-record register of Kuopio University Hospital (KUH) and nationwide register data maintained by the Social Insurance Institution of Finland (SII).

4.1.1 Hospital cohort

Included in the study were community-dwelling patients who had been diagnosed, on either an outpatient or inpatient basis, as having epilepsy between 1.1.2000 and 31.12.2013; were aged 65 or above at the time of diagnosis of epilepsy; and had their AED treatment started as monotherapy. All those patients from whom data were available from at least one follow-up visit were included. Excluded were patients who lived in institutions. In total, 529 patients meeting the inclusion criteria were identified.

A random sample of 201 patients was selected as the group of young adults from the hospital case-record register by means of the following criteria: new-onset focal epilepsy, diagnosis of epilepsy between 2000 and 2013, patient age 16–64 years at the time of diagnosis, and AED treatment begun as monotherapy.

From the KUH register we were able to review the case records of the patients and gather detailed data on the patients' medical and demographic characteristics, including the aetiology of the epilepsy and the seizure and epilepsy type. Number of seizures before AED treatment and the initial AED were recorded also, as were the patients' place of residence and marital status.

4.1.2 Register data

To study the choice of the first AED across the whole country, we collected summary-form nationwide data from the drug registers of the SII. The Drug Reimbursement Register was used to identify non-institutionalised patients who were entitled to reimbursement for AED medication after evaluation by the SII. The evaluation is based on a medical certificate, prepared by a neurologist, describing clinical, imaging and other laboratory examinations confirming the diagnosis of epilepsy. During the study period, the following drugs were subject to full reimbursement as a first-line AED: carbamazepine, oxcarbazepine, phenytoin, and valproic acid. The Drug Prescription Register of the SII covers information on drug class and the dispensing date for the prescribed medicines delivered from pharmacies and subject to reimbursement. Owing to the national health insurance covering all permanent residents in Finland, the register has good coverage of outpatient purchases of medications that require a prescription, including AED medications.

We extracted all patients aged 65 or above who had received special reimbursement for the cost of AEDs due to epilepsy in 2004 or 2012 and recorded their first AED as monotherapy during the years 2003–2004 or 2011–2012. Only those subjects who had no record of AED purchases prior to those years were included. In the 2004 cohort, 591

incident patients in the whole of Finland and in the 2012 cohort 1,081 incident patients met these criteria and were included in the study.

4.2 DEFINITIONS

For purposes of the study, epilepsy was defined as a disorder with 1) at least two unprovoked (or reflex) seizures, occurring >24 h apart; or 2) one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years on account of, for example, underlying aetiology or status epilepticus (Fisher et al. 2014).

The epilepsy was categorised as focal, generalised, or unclassified (Berg et al. 2010). Epileptic seizures were classified as focal seizures, generalised seizures, or unclassified seizures.

Refractory epilepsy is defined by ILAE (Kwan et al. 2010) as a failure of adequate trials of two tolerated, appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom. Seizure-free duration that is at least three times the longest inter-seizure interval prior to starting a new intervention would need to be observed or at least 12 months.

The aetiology of the epilepsy was recorded as stated in the case records. Patients with acute symptomatic seizures – i.e., seizures secondary to substance (including alcohol) abuse or withdrawal or due to an acute illness (Beghi et al. 2010) – were excluded.

Validated ICD-10 code algorithms were used in the KUH cohort to identify chronic comorbid conditions. The Swedish, Finnish, INteraction X-referencing (SFINX) interaction database was used to assess the possibility of clinically significant drug–AED interactions (Böttiger et al. 2009).

4.3 STATISTICAL ANALYSES

The analysis of categorical data used a chi-square test, and a Kruskal–Wallis test was used for categorical and ordinal variables. Binary logistic regression analysis was conducted to identify factors, such as age, sex, or comorbidity that might have influenced the choice of initial AED. The analysis was performed for patients whose initial AED was valproic acid ($n = 259$) or carbamazepine ($n = 164$). To estimate achievement of a cumulative probability of ≥ 2 years' or ≥ 5 years' remission, Kaplan–Meier analysis was employed. The Cox proportional hazards model was used to obtain a hazard ratio (HR) for each independent variable. The level for significance was determined to be $P < 0.05$. All statistical analyses were performed with Microsoft Excel and SPSS 21.

4.4 ETHICAL ASPECTS

This non-interventional study was based on individual-level hospital patient data, and the corresponding authorisation for using these data was received from the regulatory authority responsible for the administration of said data at KUH. The data received from the SII included no personal information of the registered subjects.

5 Results

5.1 CHOICE OF THE FIRST ANTI-EPILEPTIC DRUG (STUDY I)

In both the elderly and the young adults, there was a slight preponderance of men over women (see Table 9). The most commonly identifiable aetiologies of epilepsy in the elderly patients were stroke, central nervous system tumour, and Alzheimer's disease. In all, 51% (n = 271) of the elderly patients were married, 23% (n = 120) widowed, and 26% (n = 138) unmarried/divorced.

Table 9. Clinical and demographic characteristics of the hospital-patient group with newly diagnosed epilepsy

	Elderly		Young adults	
Sex				
Women	253	48 %	Women	84 42 %
Men	276	52 %	Men	117 58 %
Age				
65-69	121	23 %	16-19	16 8 %
70-74	143	27 %	20-29	30 15 %
75-79	99	19 %	30-39	21 10 %
80-84	112	21 %	40-49	51 25 %
85-89	46	9 %	50-59	55 27 %
90-94	8	2 %	60-64	28 14 %
Epilepsy type				
Focal	527	100 %	Focal	201 100 %
Unclassified	2	0 %	Unclassified	0 0 %
Aetiology of epilepsy				
Stroke	237	45 %	Stroke	33 16 %
CNS tumour	54	10 %	CNS tumour	29 14 %
Alzheimer's disease	44	8 %	Alzheimer's disease	0 0 %
Head injury	10	2 %	Head injury	14 7 %
CNS infection	6	1 %	CNS infection	7 3 %
Other	9	2 %	Other	26 13 %
Unknown	169	32 %	Unknown	92 46 %
Total	529		201	

CNS = central nervous system

5.1.1 The choice of the first anti-epileptic drug

Among the hospital-group patients, there were statistically significant differences in the choice of first AED between the elderly patients and young adults ($p < 0.001$; see Table 10). The main difference was in the frequency of prescription of carbamazepine and valproic acid.

Table 10. Choice of the first anti-epileptic drug in the elderly and in young adult patients identified from the hospital

	Elderly		Young adults	
	N	n	n	%
Valproic acid	259	49 %	39	19 %
Carbamazepine	164	31 %	122	61 %
Levetiracetam	39	7 %	12	6 %
Phenytoin	20	4 %	0	0 %
Oxcarbazepine	15	3 %	18	9 %
Lamotrigine	15	3 %	6	3 %
Gabapentin	14	3 %	2	1 %
Pregabalin	2	0 %	2	1 %
Clobazam	1	0 %	0	0 %
Total	529		201	

The choice of the first AED in the elderly patients varied statistically significantly ($p < 0.001$) with the age group (see Figure 8). With advancing age, the proportion of valproic acid increased while that of carbamazepine decreased.

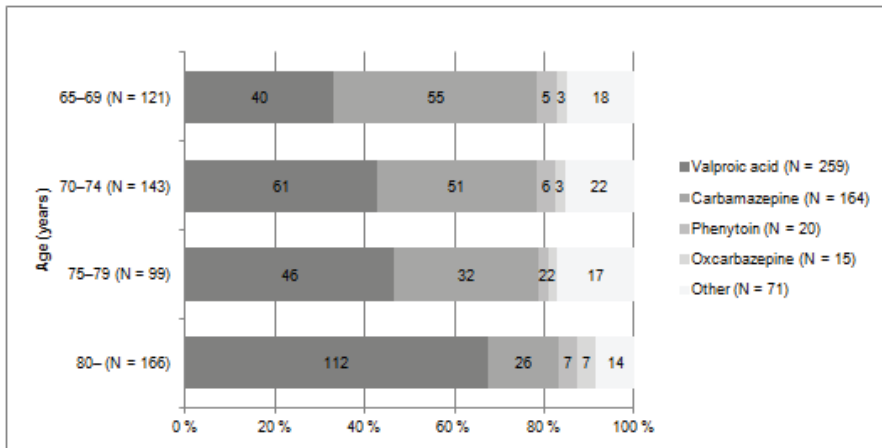


Figure 8. The choice of the first anti-epileptic drug, by the patient's age group.

Predictive factors for the choice of carbamazepine and valproic acid as the initial AED were analysed via binary logistic regression analysis (see Table 11).

Table 11. Predictors of the choice of the initial anti-epileptic drug in the elderly patients with newly diagnosed epilepsy

Valproic acid (n = 259)						Carbamazepine (n = 164)					
Variable	Odds ratio	95% confidence interval	P-value	Variable	Odds ratio	95% confidence interval	P-value				
Age	1.085	1.054–1.117	<0.001	Age	0.921	0.892–0.951	<0.001				
Sex	1.443	0.996–2.091	0.053	Sex	0.682	0.457–1.017	0.060				
Comorbidity				Comorbidity							
Diabetes	1.026	0.658–1.597	0.911	Diabetes	1.884	1.113–3.190	0.018				
Hypertension	0.704	0.482–1.029	0.704	Hypertension	1.219	0.814–1.825	0.336				
Osteoporosis	0.584	0.280–1.221	0.153	Osteoporosis	1.493	0.655–3.403	0.340				
Myocardial infarction / bypass / PTCA	2.110	1.284–3.469	0.003	Myocardial infarction / bypass / PTCA	0.353	0.185–0.674	0.002				
Atrial fibrillation	0.704	0.482–1.029	0.070	Atrial fibrillation	1.621	1.011–2.598	0.045				
Any cancer	0.744	0.474–1.169	0.200	Any cancer	0.899	0.550–1.470	0.672				
Ischaemic stroke / intracerebral haemorrhage	1.549	1.098–2.187	0.013	Ischaemic stroke / intracerebral haemorrhage	0.928	0.640–1.345	0.692				
PTCA = percutaneous transluminal coronary angioplasty											

Statistically significant predictors for the choice of valproic acid as initial AED were myocardial infarction and ischaemic stroke or haemorrhage. A predictor for lower possibility of receiving carbamazepine as first AED was myocardial infarction, whereas diabetes and atrial fibrillation predicted a higher probability of receiving carbamazepine.

5.1.2 Number and characteristics of seizures prior to treatment start

More than half of the elderly patients had experienced one or two seizures before AED treatment. There were no statistically significant differences in the total number of pre-treatment seizures or in the number of focal generalised seizures between age groups.

A large majority of the elderly patients (427 patients, 81%) had focal generalised seizures, and 137 (26%) of the patients overall had focal seizures without generalisation (see Figure 9). In 35 (7%) of the patients, both focal seizures without generalisation and focal generalised seizures had occurred before AED treatment. Because the sets overlap, the percentages sum to above 100%. The number of seizures prior to the start of AED treatment was statistically significantly higher ($p < 0.001$) among patients with focal seizures without generalisation than the number in patients who experienced focal seizures with generalisation.

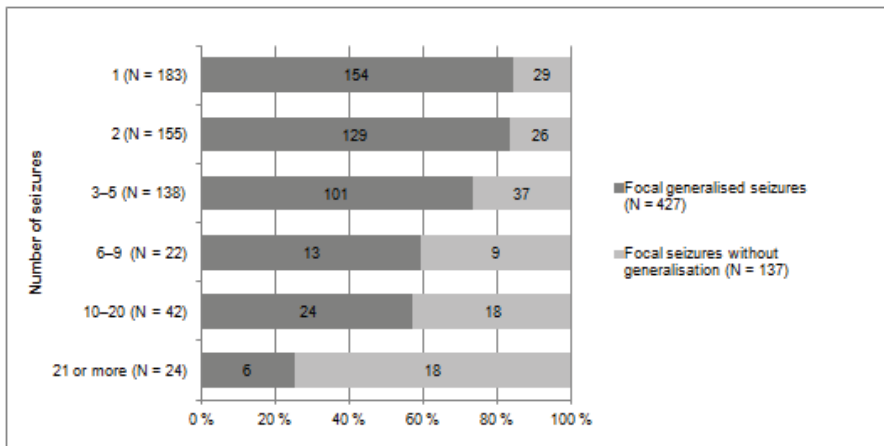


Figure 9. The number of focal seizures prior to the start of anti-epileptic drug treatment.

5.1.3 Time trends of initial AED choices

There was statistically significant ($p < 0.001$) variation in the choice of AEDs over the observation period both in the elderly hospital-group patients and in the whole-country dataset (see Table 12). In both hospital-patient and whole-country data, the prevalence of choice of carbamazepine and phenytoin as the first AED decreased and that of choosing valproic acid and levetiracetam increased over the span of the years examined. In the nationwide data, the use of oxcarbazepine was more frequent than it was in the KUH patients.

Table 12. The choice of the first anti-epileptic drug during different time periods in the elderly hospital-based with epilepsy and in the national register data (the 'Other AED' category includes the anti-epileptic clobazam in the KUH data and clobazam, clonazepam, lacosamide, tiagabine, and topiramate in the whole-country data)

KUH	2000–2004		2005–2009		2010–2013		National register		2004		2012	
	N	%	N	%	N	%	N	%	N	%	N	%
Valproic acid	45	28 %	110	57 %	104	60 %	Valproic acid	60 %	146	25 %	363	34 %
Carbamazepine	82	51 %	52	27 %	30	17 %	Carbamazepine	17 %	150	25 %	179	17 %
Levetiracetam	1	1 %	11	6 %	27	16 %	Levetiracetam	16 %	0	0 %	108	10 %
Phenytoin	17	10 %	3	2 %	0	0 %	Phenytoin	0 %	83	14 %	26	2 %
Oxcarbazepine	3	2 %	6	3 %	6	3 %	Oxcarbazepine	3 %	185	31 %	278	26 %
Lamotrigine	11	7 %	0	0 %	4	2 %	Lamotrigine	2 %	8	1 %	11	1 %
Gabapentin	3	2 %	10	5 %	1	1 %	Gabapentin	1 %	11	2 %	17	2 %
Pregabalin	0	0 %	1	1 %	1	1 %	Pregabalin	1 %	0	0 %	78	7 %
Other AED	0	0 %	0	0 %	1	1 %	Other AED	1 %	8	1 %	21	2 %
Total	162		193		174		Total		591		1081	

5.2 OUTCOME OF INITIAL ANTIEPILEPTIC DRUG TREATMENT (STUDY II)

5.2.1 The outcome of initial monotherapy

A total of 315 patients (59%) became seizure free with the first monotherapy and the treatment was stopped in 190 (36%) patients either due to lack of efficacy or adverse effects (Figure 10). The mean time to stopping of the first AED because of lack of efficacy was 14 months (median: 7.2 months) and due to adverse events it was 8.1 months (median: 2.5 months). In all, 141 of the cases with failure to the first AED were switched to another monotherapy, while 49 patients began combination treatment with AEDs. After the second AED monotherapy regimen, combination treatment with AEDs was started for 15 patients, and for two patients it was started after a third monotherapy regimen.

There were no statistically significant differences in the response to treatment for the first, second, and third monotherapy regimens (Figure 10).

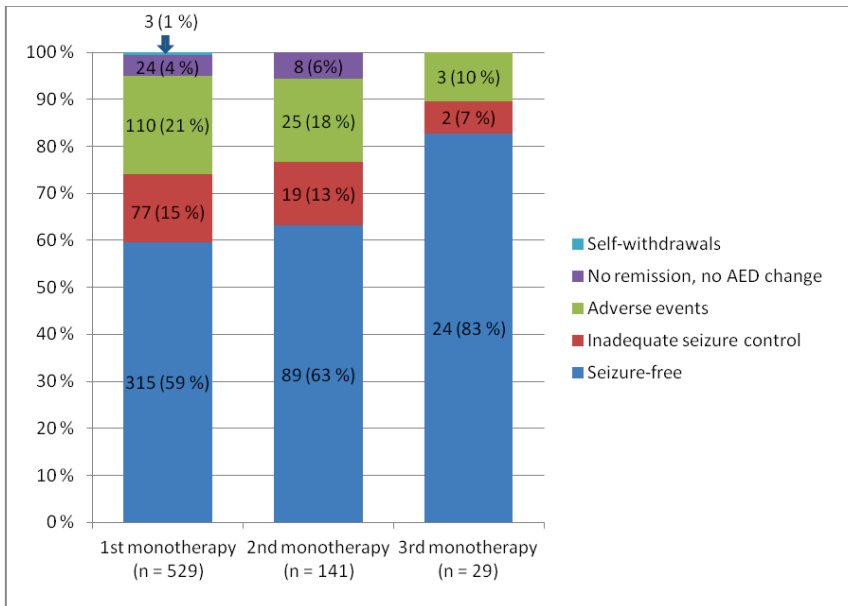


Figure 10. Response to successive monotherapy regimens of antiepileptic drugs in elderly patients with newly diagnosed epilepsy.

Response to the second monotherapy was similar between patients whose first monotherapy failed because of intolerable adverse effects and those with failure due to inadequate seizure control (Figure 11). No remission, no AED change means that patient did not achieve seizure remission but still the AED treatment was not changed.

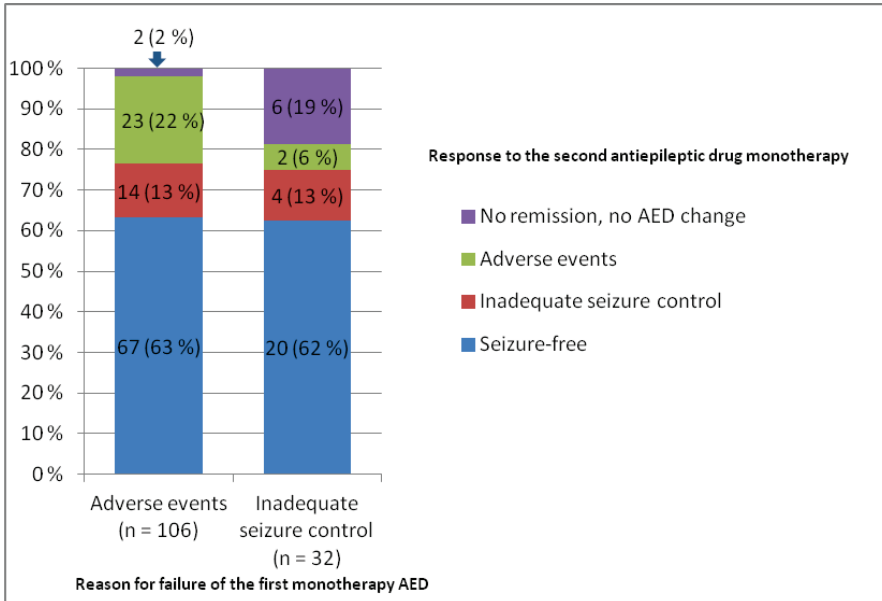


Figure 11. Response to the second antiepileptic drug monotherapy, by reason for the failure of the first monotherapy regimen using an antiepileptic drug.

We also analyzed the outcome of initial monotherapy with carbamazepine and valproic acid, the most common choices for the first AED in this population. Probability for the withdrawal of initial carbamazepine treatment due to lack of efficacy was statistically significantly lower ($p = 0.032$) than that for valproic acid (Figure 12). On the other hand, probability for withdrawal due adverse effects was significantly higher ($p < 0.001$) for carbamazepine than for valproic acid (Figure 13).

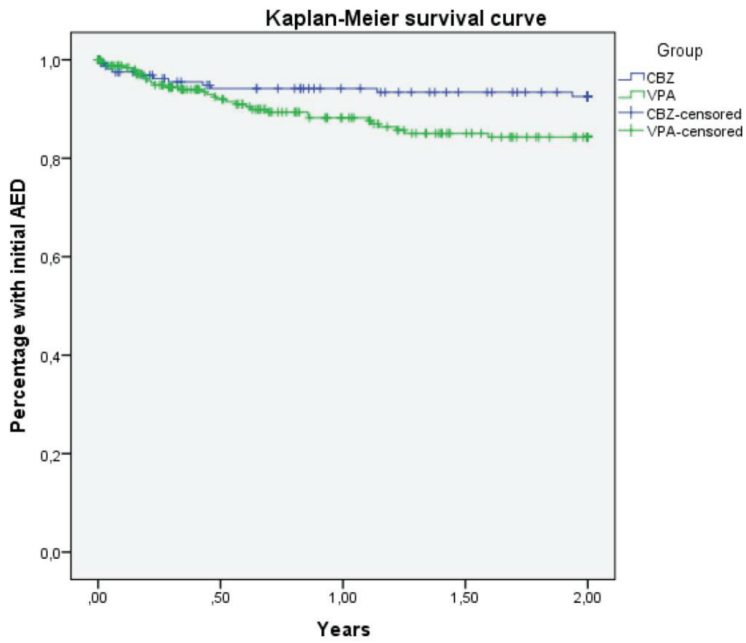


Figure 12. Kaplan-Meier estimate of cumulative probability of withdrawal of valproic acid (n = 259) or carbamazepine (n = 164) because of lack of efficacy.

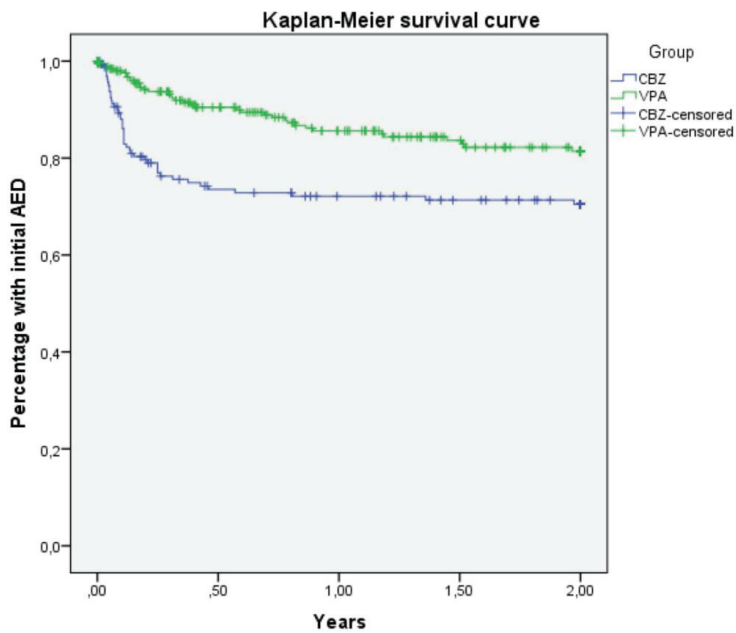


Figure 13. Kaplan-Meier estimate of cumulative probability of withdrawal of valproic acid (n = 259) or carbamazepine (n = 164) because of adverse effects.

In all, 339 (64%) of the patients used the initial AED for the entire follow-up period, while the treatment was changed for 190 (36%) of the patients. Of the 164 patients with initial carbamazepine treatment, 36 (22%) were switched to valproic acid, 12 (7%) to other AED monotherapy, and 9 (5%) to AED combination regimen. In 259 patients started on valproic acid the drug was changed to carbamazepine (7, 3%) or other AED monotherapy (n = 40, 15%). Furthermore, in 26 (10%) of the patients, combination treatment was initiated. In total, 456 patients (86%) from the sample of 529 were treated with monotherapy at the end of follow-up.

Altogether 22 (4%) of all patients did not achieve at least 12-month remission with the second AED treatment (monotherapy or polytherapy) and, accordingly, were classified as having refractory epilepsy.

5.2.2 Long-term outcome of seizures

Follow-up data for at least two years were available for 293 patients (55% of the total population) and for at least five years from 132 (25%). The estimated cumulative probabilities of achieving ≥ 2 years' and ≥ 5 years' terminal remission were 83% and 79%, respectively ($p < 0.001$) (Figure 14). Breakdown of the outcome of seizures in the 293 patients is presented in Figure 15. Almost of half of the patients remained seizure-free with their first AED. The epilepsy was classified as refractory on 15 patients whose follow-up data was available at least for two years.

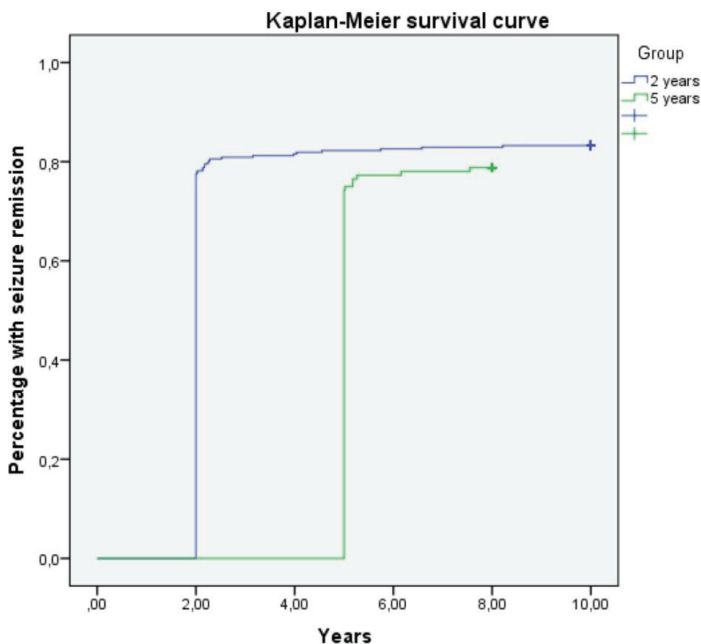


Figure 14. Kaplan-Meier estimate of cumulative probability of achieving two or more years' (n = 293) or five or more years' (n = 132) seizure remission during antiepileptic drug treatment.

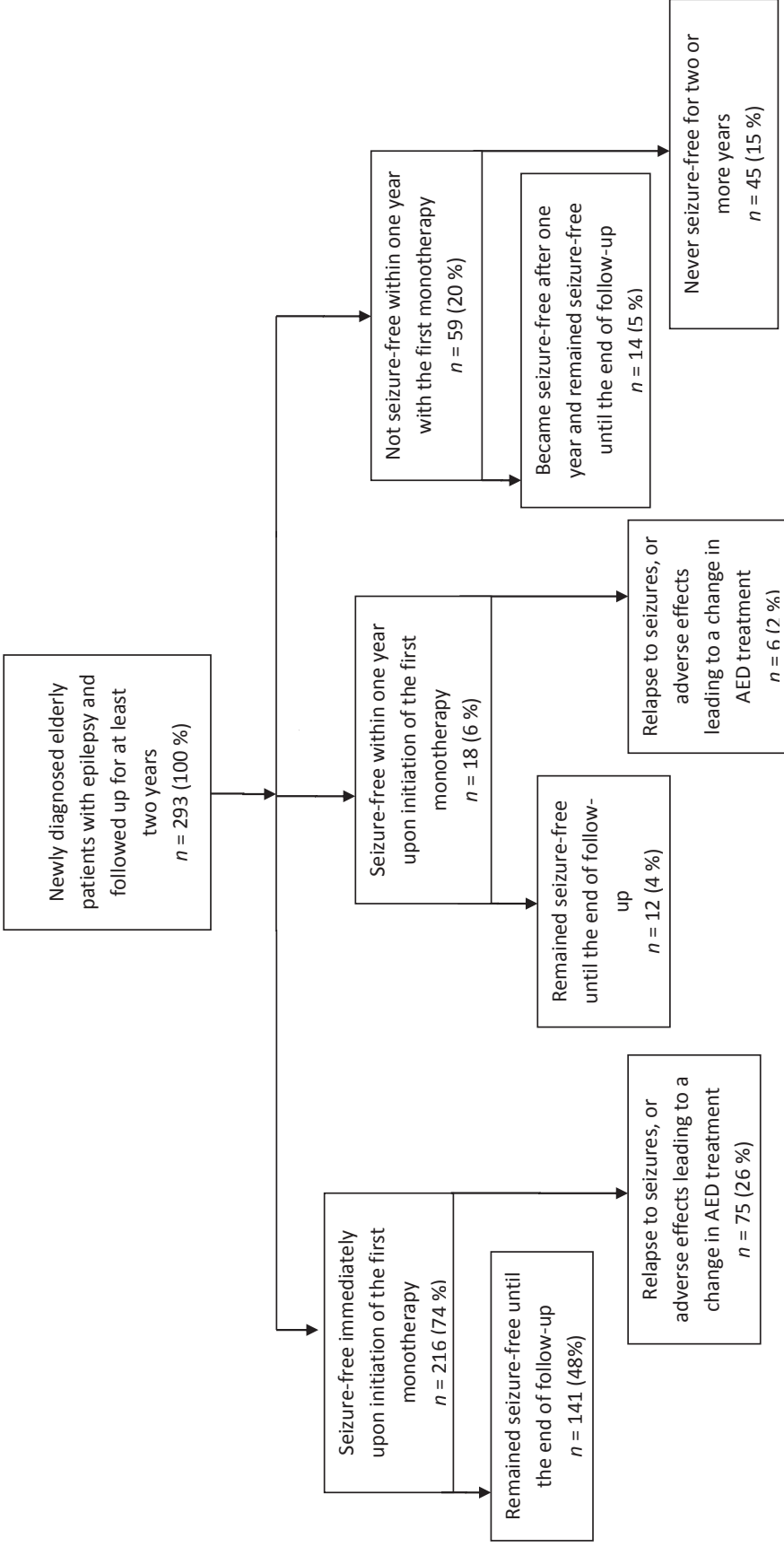


Figure 15. Breakdown of the seizure outcome with antiepileptic drug treatment in elderly patients with newly diagnosed epilepsy and followed for at least two years.

5.2.3 Predictors of remission

The predictive value of gender and various clinical parameters for achieving at least two years' remission of seizures, as assessed via the Cox proportional hazards model, is shown in Table 13. Only early treatment response – i.e., whether or not remission was achieved within one year after the start of the first AED – was a statistically significant predictor of remission.

Table 13. Predictive factors for at least two-year remission of seizures

Characteristic	HR	95% CI	P
Sex			
Male	1	-	-
Female	0.93	0.724–1.194	0.568
Age at diagnosis (years)			
<70	1	-	-
70–79	1.075	0.795–1.455	0.637
≥80	1.111	0.789–1.566	0.546
Aetiology			
Unknown	1	-	-
Known	0.889	0.690–1.146	0.365
EEG pretreatment			
Normal	1	-	-
Abnormal non-epileptiform	1.085	0.778–1.515	0.630
Epileptiform	0.912	0.531–1.565	0.738
Seizure type			
Focal generalised seizures	1	-	-
Focal seizures	0.993	0.741–1.330	0.962
Number of seizure types			
Single seizure type	1	-	-
Two seizure types	0.832	0.508–1.362	0.464
Number of seizures prior to AED treatment			
1	1	-	-
2–5	1.138	0.849–1.525	0.388
6–9	1.308	0.722–2.371	0.376
≥10	1.049	0.698–1.578	0.817
Time from first seizure to initiation of the first AED			
<3 months	1	-	-
3–5 months	0.946	0.630–1.421	0.790
>5 but <12 months	0.932	0.519–1.674	0.814
≥12 months	1.008	0.714–1.423	0.963
Seizure remission after initiation of the first AED			
Achieved within one year	1	-	-
Not achieved within one year	0.011	0.003–0.044	<0.001

5.3 CO-MORBIDITY AND CLINICALLY SIGNIFICANT INTERACTIONS BETWEEN AED AND OTHER DRUGS (STUDY III)

5.3.1 Co-morbid conditions and the frequency of polypharmacy

The most common co-morbidities in the hospital cohort of 529 elderly patients were hypertension, dyslipidemia, and coronary heart disease (Table 14).

Table 14. Concomitant disorders among the hospital cohort of elderly patients with epilepsy.

	Total n = 529 n (%)	Carbamazepine n = 164 n (%)	Valproic acid n = 259 n (%)	Other antiepileptic drugs n = 106 n (%)
Cardiovascular disorders				
Hypertension	338 (64)	101 (62)	182 (70)	55 (53)
Coronary heart disease	176 (33)	42 (26)	104 (40)	30 (29)
(History of) myocardial infarction	43 (8)	9 (5)	26 (10)	8 (8)
Atrial fibrillation	132 (25)	30 (18)	74 (29)	28 (27)
Heart failure	42 (8)	11 (7)	27 (10)	4 (4)
Ischaemic stroke	183 (35)	54 (33)	107 (41)	22 (21)
Intracerebral haemorrhage	52 (10)	20 (12)	27 (10)	5 (5)
Metabolic or endocrine disorders				
Dyslipidemia*	236 (47)	71 (43)	129 (50)	48 (47)
Diabetes (types I and II)	99 (19)	22 (13)	51 (20)	26 (25)
Hypothyroidism	71 (13)	25 (15)	30 (11)	16 (15)
Other disorders				
Asthma	61 (12)	17 (10)	31 (12)	13 (13)
Any extracerebral cancer	74 (14)	21 (13)	32 (12)	21 (20)
Brain tumour	54 (10)	19 (12)	19 (7)	16 (15)

* Patients treated with statins

The median number of non-AED-type drugs in this patient population was 7 (mean: 7.64). Polypharmacy (i.e., at least six concomitant drugs) was found in 366 patients (69%) and excessive polypharmacy (10 or more concomitant drugs) in 145 (27% of the patients).

5.3.2 Major interactions between the AEDs and non-AEDs

The most common of the major interactions ((i.e., those in classes C and D) were seen for carbamazepine with dihydropyridine calcium-channel blockers, simvastatin, warfarin, antipsychotics, and diazepam (Table 15).

In the hospital cohort, 52 subjects (32%) started on carbamazepine had one class-C or class-D interaction with other drugs, and 51 subjects (31%) had two or more class-C or class-D interactions. The corresponding frequencies in the nationwide population were 42% and 23%, respectively. In the hospital cohort, only 2% of the subjects started on valproate had a class-C interaction. None of the subjects with oxcarbazepine showed interactions, of either class.

Table 15. Frequency of clinically meaningful drug interactions between three antiepileptic drugs and other drugs in the elderly patients with newly diagnosed epilepsy.

	Carbamazepine		Valproic acid		Oxcarbazepine	
	KUH (n = 164)	SII (n = 179)	KUH (n = 259)	SII (n = 363)	KUH (n = 15)	SII (n = 278)
Cardiovascular drugs						
Dihydropyridine calcium blockers						
Nifedipine	4 2%	3 2%	6 2%	1 0%	0 0%	3 1%
Felodipine	12 7%	3 2%	21 8%	9 2%	3 20%	10 4%
Lercanidipine	8 5%	5 3%	9 3%	13 4%	0 0%	5 2%
Diltiazem	2 1%	1 1%	3 1%	2 1%	0 0%	0 0%
Statins						
Atorvastatin	12 7%	14 8%	26 10%	45 12%	0 0%	24 9%
Simvastatin	44 27%	44 25%	83 32%	78 21%	5 33%	75 27%
Lovastatin	0 0%	0 0%	4 2%	1 0%	0 0%	2 1%
Haematological agents						
Warfarin	26 16%	20 11%	92 36%	55 15%	4 27%	50 18%
Central nervous system agents						
Tricyclic antidepressants						
Amitriptyline	2 1%	0 0%	6 2%	0 0%	0 0%	1 0%
Doxepin	1 1%	0 0%	1 0%	3 1%	0 0%	0 0%
Serotonin-selective reuptake inhibitors						
Citalopram	22 13%	6 3%	29 11%	19 5%	2 13%	11 4%
Fluoxetine	0 0%	2 1%	1 0%	0 0%	0 0%	1 0%
Antipsychotics						
Haloperidol	3 2%	0 0%	10 4%	3 1%	0 0%	1 0%
Quetiapine	5 3%	4 2%	37 14%	26 7%	0 0%	6 2%
Risperidone	14 9%	4 2%	20 8%	21 6%	0 0%	9 3%
Olanzapine	0 0%	0 0%	1 0%	4 1%	0 0%	2 1%
Benzodiazepines						
Diazepam	5 3%	16 9%	6 2%	30 8%	0 0%	13 5%
Opiates						
Oxycodone	2 1%	0 0%	9 3%	5 1%	1 7%	2 1%
Codeine	4 2%	6 3%	5 2%	13 4%	0 0%	11 4%
Tramadol	4 2%	2 1%	7 3%	3 1%	0 0%	7 3%

Green (class A): No data on any clinically relevant drug–drug interaction

Grey (class B): An interaction of minor clinical importance

Yellow (class C): Clinically relevant interaction that can be handled via, for example, dose adjustments (the interaction has been documented in controlled studies in appropriate patient populations)

Red (class D): Clinically relevant interaction – combining the drugs should be avoided (the interaction has been documented in controlled studies in appropriate patient populations)

KUH = Kuopio University Hospital

SII = Social Insurance Institution of Finland

With the hospital cohort's data, we evaluated whether the frequencies of the major classes of interaction in non-AED cases were different between subjects treated with enzyme-inducing AEDs (carbamazepine, oxcarbazepine, and/or phenytoin) and those treated with non-enzyme-inducing AEDs (valproate, gabapentin, lamotrigine, levetiracetam, and clobazam). There was a trend toward a two-times lower frequency of warfarin use among the patients starting an enzyme-inducing AED (Table 16). However, no statistically significant difference in the distribution of other drugs between the two AED classes was observed.

Table 16. The choice of enzyme-inducing antiepileptic drugs and non-enzyme-inducing drugs and the major non-antiepileptic drug classes in the 529 hospital-cohort patients

Concomitant drug	Enzyme-inducing AED (n=199)	Non-enzyme-inducing AED (n=330)
Dihydropyridine calcium channel blockers	48 (24%)	92 (28%)
Statins	77 (39%)	159 (48%)
Warfarin	37 (19%)	125 (38%)
Antidepressants	30 (15%)	58 (18%)
Antipsychotics	28 (14%)	77 (23%)

5.4 SUMMARY OF THE RESULTS

- I Valproic acid and carbamazepine were the most common initial AEDs both among the elderly (49% and 31% of prescriptions, respectively) and for the patients in the younger-adults group (19% and 61%, respectively) in the KUH data. In the nationwide register data, the most frequently used initial AEDs for the elderly were valproic acid and oxcarbazepine. The selection of valproic acid was associated with higher age ($P < 0.001$), myocardial infarction ($P = 0.003$), and stroke ($P = 0.013$). Lower probability of receiving carbamazepine was observed with more advanced age ($P < 0.001$) and myocardial infarction ($P = 0.002$), whereas diabetes ($P = 0.018$) and atrial fibrillation ($P = 0.045$) predicted a higher probability.
- II All told, 336 (64%) of the patients used the initial AED for the whole follow-up period, while the treatment was changed for 193 (36%) of the patients. In total, 456 (86%) of the 529 patients were treated with monotherapy until the end of follow-up. Four per cent of the patients developed refractory epilepsy. The response to the second monotherapy after failure of the first monotherapy was similar between patients whose treatment failed for reason of intolerable adverse effects and those showing failure due to inadequate seizure control. The estimated cumulative probability of achieving ≥ 2 years' remission was 83%, and that for achieving ≥ 5 years of remission was 79%. Early response to treatment was a statistically significant predictor of remission.
- III Hypertension (67%), dyslipidemia (45%), and ischaemic stroke (32%) were the most common co-morbid conditions in the hospital cohort of patients. In these patients, excessive polypharmacy (more than 10 concomitant drugs) was identified in 27% of cases. Of the patients started on carbamazepine, 52 subjects (32%) had one class-C or class-D drug interaction and 51 (31%) had two or more C- or D-class interactions. Only 2% of the subjects started on valproate exhibited a class-C interaction. None of the subjects using oxcarbazepine displayed class-C or class-D interactions. The most common drugs with potential interactions with carbamazepine were dihydropyridine calcium-blockers, statins, warfarin, and psychotropic drugs.

6 Discussion

6.1 CHOICE OF THE FIRST ANTI-EPILEPTIC DRUG (STUDY I)

According to our population-based data, valproic acid has gained the position of the most popular first AED for elderly patients with newly diagnosed epilepsy in Finland. Furthermore, the data based on hospital patient records showed that, with advancing patient age, the proportion of valproic acid to all AEDs prescribed rose. In comparison with practices in the US (Pugh et al. 2011; Ruggles et al. 2001) the use of phenytoin was quite limited in Finland. The Finnish guidelines on the treatment of epilepsy (Kälviäinen et al. 2014) state that, because of its adverse effects and the challenges in pharmacokinetics, phenytoin should not be used as first-line AED for adult patients. According to the relevant guideline, valproic acid is not recommended as the first choice for focal epilepsy. However, it may have been favoured for our patients on account of its lack of adverse cardiac effects, hepatic metabolic enzyme induction, lower risk of drug interactions relative to carbamazepine, and good tolerability in the elderly (Stephen & Brodie 2000; Stephen et al. 2006).

Most of the new-onset seizures in the elderly have focal onset (Cloyd et al. 2005). In the hospital-patient cohort, almost all cases had a diagnosis of focal epilepsy. Cerebrovascular disorders were the most common aetiology of epilepsy in our patients, a finding consistent with previous observations (Stephen & Brodie 2000). In about one third of cases, the aetiology of the epilepsy remained unknown.

A third of the patients identified from the hospital had experienced a single seizure and 28% two seizures before AED treatment commenced, which indicates an active approach to the treatment of epilepsy in the elderly. Patients with focal generalised seizures usually had only one (36%) or two (30%) seizures before AED treatment, whereas two thirds of the patients with focal seizures without generalisation had experienced more than two seizures before treatment commenced. This probably is linked to difficulties in the diagnosis of epilepsy in the elderly. If focal seizures without generalisation are not recognised as epileptic in nature by the patients or family or the symptoms do not cause significant impairment to the patient's life, consultation of a physician and also diagnosis may be delayed.

In the hospital-based cohort, there were differences in the choice of initial AED between the elderly patients and young adults treated: in total, 61% of the latter were prescribed carbamazepine. This frequency is twice that for the elderly. In young adults, valproic acid was the second most commonplace initial choice, followed by oxcarbazepine. The choices for young adults are in accordance with other studies' findings (Glauser et al. 2013).

According to our study, concomitant disorders seemed to have some impact on the choice of initial AED: carbamazepine use was started less often in cases of patients with cardiac disorders, and valproic acid was favoured for patients with diagnosed myocardial infarction or stroke. In the binary logistic regression analysis, cardiac disorders were found to be an independent predictive factor for the choice of both carbamazepine and valproic acid. Valproic acid has been reported to be associated with lower risk of myocardial

infarction and stroke as compared with carbamazepine (Dregan et al. 2014; Olesen et al. 2011). Because of the high prevalence of cardiovascular comorbidity in the elderly patients with epilepsy and risk of drug interactions with carbamazepine, valproic acid was favoured over carbamazepine in the oldest age groups. The reason for favouring of carbamazepine in patients with diabetes remains obscure.

The choices for initial AEDs for community-dwelling elderly patients with epilepsy, identified from the hospital, deviated from the prescription pattern for the country at large with respect to use of carbamazepine and oxcarbazepine: according to the whole-country register data, oxcarbazepine, which was approved for use as monotherapy more than 20 years ago in Finland, was more popular than carbamazepine. Oxcarbazepine is more strongly associated with hyponatraemia than carbamazepine is (Stephen and Brodie 2000), which may account for its lower popularity for elderly hospital-group patients. Internationally, carbamazepine remains one of the AEDs most commonly used for the elderly (Karlsson et al. 2014; Pugh et al. 2011).

Pugh et al. (2008; 2011) observed some time-related trends in the choice of AEDs in the United States: from 2000 to 2006, the use of phenytoin declined and the frequency of use of carbamazepine, gabapentin, and valproic acid remained quite stable, but the use of levetiracetam increased. In our study, valproic acid and levetiracetam became more popular whilst the use of carbamazepine declined over the last 12 years. With the exception of levetiracetam, second-generation AEDs were used only in the minority of cases in both the elderly-hospital-patients cohort and the nationwide material, despite the fact that gabapentin and lamotrigine have shown established evidence of efficacy in elderly patients (Brodie et al. 1999; Rowan et al. 2005; Werhahn et al. 2015). The prescription pattern in Finland most probably is related to the fact that, with the exception of oxcarbazepine, second-generation AEDs are not subject to full reimbursement as first-line drugs.

Management of epilepsy in the elderly requires an understanding of aetiology and pharmacological factors that are unique to older persons (Cloyd et al. 2005; Stephen & Brodie 2000). The choice of AED should be based on assessment of seizure type, concomitant medications, and coexisting diseases. Because newer AEDs may have fewer or less severe interactions and side effects when compared to standard AEDs, they might be more suitable as a treatment of first choice for the elderly (Bergey et al. 2004; Stephen & Brodie 2000).

6.2 OUTCOME OF INITIAL ANTIEPILEPTIC DRUG TREATMENT (STUDY II)

In this study of community-dwelling elderly subjects with newly diagnosed epilepsy, most of the patients were successfully treated with monotherapy – in fact, 64% with their first AED for the whole follow-up period. Success of monotherapy has been observed also in previous studies of newly diagnosed elderly subjects with epilepsy (Besocke et al. 2013; Stephen et al. 2006; Tanaka et al. 2013). In adolescents and adults with newly diagnosed epilepsy, it has been reported that response to successive monotherapy regimens showed lower success rates as the number of trials increased (Mohanraj & Brodie 2006). This was not the case for our patients, who showed similar remission rates after the first, second, and third monotherapy regimen. Our findings may have been influenced by the fact that quite a few patients were shifted to combination AED treatment after each monotherapy trial. Previous studies have found that the response to the second monotherapy drug may be better in those patients whose treatment failed for reason of adverse effects than in those with lack of efficacy (Kwan & Brodie 2000a; Mohanraj & Brodie 2006). This was not seen in our elderly patients, possibly on account of the change in therapy to combination treatment for many patients with inadequate response to treatment.

Terminal seizure-freedom for at least two or five years was observed in 83% and 79%, respectively. Furthermore, almost half (48%) of the full cohort followed up on for at least two years did not experience any seizures after the start of treatment with an AED. This proportion is considerably higher than the 31% previously observed in adolescent and adult patients with newly diagnosed epilepsy (Mohanraj & Brodie 2005, 2006). In previous, hospital-based studies, with smaller sample sizes and shorter follow-up times, 70–96% of the patients were seizure-free for at least one year and 67% for at least two years (Besocke et al. 2013; Stephen et al. 2006; Tanaka et al. 2013). Taken together, these data suggest that the outcome for seizures in elderly patients diagnosed with epilepsy is good.

We explored the predictive value of several clinical factors for the probability of reaching remission of seizures. Of the factors considered, only the treatment response within one year from the start of AED treatment was a statistically significant predictor according to the multivariate analysis. This finding is consistent with previous studies in both community and hospital-based populations with epilepsy (Annegers et al. 1979; Elwes et al. 1984; Kwan & Brodie 2000b). Gender, age at onset of epilepsy, and EEG did not predict the outcome for seizures, as has been observed also by Besocke et al. (2013) and Stephen et al. (2006) in elderly patients. In contrast to previous findings (Besocke et al. 2013; Stephen et al. 2006), those of our patients with a structural aetiology or high number of pretreatment seizures did not have a worse prognosis. Because of the small number of subjects who did not enter remission in our study, it may have lacked sufficient statistical power to show differences in some parameters.

Treatment of epilepsy in the elderly may be complicated by several factors, such as comorbidity and co-medication, which could lower the tolerability of AEDs (Besocke et al. 2013). In 21% of our patients, there was a switch from the first AED because of adverse effects, a higher frequency than the 12% reported by Stephen et al. (2006). Clinical trial results suggest that differences may exist in the tolerability of AEDs among the elderly and

that second-generation AEDs such as lamotrigine and levetiracetam may be better tolerated than carbamazepine (Rowan et al. 2005; Werhahn et al. 2015). Almost half of our patients had valproic acid and a third carbamazepine as their first AED. Differences in the outcome of the two drugs were quite modest: carbamazepine was withdrawn less often than valproic acid due to lack of efficacy, but the withdrawal rate due to adverse effects was higher with carbamazepine compared with valproic acid.

6.3 CO-MORBIDITY AND CLINICALLY SIGNIFICANT INTERACTIONS BETWEEN AED AND OTHER DRUGS (STUDY III)

The results of the study highlight the importance of recognising possible interactions of AEDs with other drugs in elderly people with newly diagnosed epilepsy if we are to avoid toxicity or worsening of concomitant conditions.

Only a few studies to date have evaluated co-morbidity in patients with recent late-onset epilepsy (Phabphal et al. 2013; Pugh et al. 2010; Stefan et al. 2014). The prevalence figures for hypertension (67%), diabetes (18%), and a history of myocardial infarction (7%) in our hospital patients were quite similar to those reported by Stefan et al. in 2014 (71%, 15%, and 9%, respectively), but coronary heart disease was markedly more frequent in our patients (32%) than in the German patient population (10%). Hypertension (87%), heart disease (46%), diabetes (39%) and hypercholesterolaemia (58%) were more frequent in the patient population of Pugh et al. (2010) as compared with our hospital cohort. A possible explanation for the difference in findings may be that 98% of the patients in Pugh et al.'s study were male. Also, the reported prevalence of somatic co-morbidity, including hypertension (4%), coronary artery disease (5%), and diabetes (4%), was low in a study conducted in Thailand (Phabphal et al. 2013). The difference relative to Western populations may be related to lifestyle and genetic factors.

Co-morbidities may lead to a risk of polypharmacy. In our hospital cohort of elderly patients with newly diagnosed epilepsy, the frequency of polypharmacy was 69% when we used the widely applied criterion of at least six concomitant drugs. The frequency of polypharmacy in our epilepsy cohort was higher than the 57% observed in a general elderly community-dwelling population from the same geographical area (Jyrkkä et al. 2009). Also, Gidal and colleagues observed in 2009 that patients with epilepsy were more likely to have more concomitant medications than the general population and that the number of other drugs increased with age.

Recognition of co-morbidity in newly diagnosed patients with epilepsy is important for assessing the risk of drug interactions. Possible pharmacokinetic interactions with AEDs and many other drugs have been described well (Zaccara & Perucca 2014), but only a few previous studies have examined the risk of clinically relevant interactions in cohorts of patients with epilepsy (Gidal et al. 2009, Pugh et al. 2010). Gidal et al. (2009) analysed medical and pharmaceutical claims data from the United States to identify exposure to new non-AED-type drugs that were started after initiation of an AED for patients of all ages. In their data, phenytoin and carbamazepine were the most common AEDs in elderly patients. Statins, calcium-channel blockers, and selective serotonin re-uptake inhibitors were the most frequently used other drugs, especially among the elderly (Gidal et al. 2009). Pugh et al.'s 2010 study used national databases of the Veterans Health Administration in the United States to assess possible drug interactions in elderly subjects with newly diagnosed epilepsy. In their dataset, phenytoin and carbamazepine were the most commonly prescribed AEDs, constituting 77% of all AEDs. Pugh et al. found that 58% of the patients on phenytoin and 56% of those on carbamazepine received a concomitant drug with

potential for clinically significant interaction with AEDs, most commonly statins, felodipine, metoprolol, oral anticoagulants, and psychotropic drugs. In findings consistent with those of Pugh and colleagues, we found that almost two thirds of the patients started on carbamazepine had at least one potentially significant drug interaction and that the most common interacting drugs were calcium-channel blockers, simvastatin, warfarin, antidepressants, and antipsychotics.

Exposure to carbamazepine in patients undergoing felodipine, warfarin, or risperidone treatment may be associated with a significant or even dramatic loss of bioavailability and therapeutic response (Capewell et al. 1988; Hansen et al. 1971; Spina et al. 2000). Furthermore, reports have described the possibility of the bioavailability and efficacy of simvastatin, fluvastatin, and atorvastatin being compromised in some patients taking potent enzyme-inducing drugs such as carbamazepine and phenytoin (Murphy et al. 1999; Ucar et al. 2004). Data from Norway and the United States suggest that the risk of interaction between enzyme-inducing AEDs and statins may be overlooked (Gedde-Dahl et al. 2012; Mintzer et al. 2014). Furthermore, it has been shown that blood cholesterol in subjects on carbamazepine is higher than that in control subjects.

It is firmly established that pharmacokinetic drug–drug interactions are associated with enzyme-inducing AEDs (Zaccara & Perucca 2014). However, supporting the findings of Gidal et al. (from 2009), we found that the distribution of major classes of other drugs was similar between patients who started an enzyme-inducing and a non-enzyme-inducing AED. There was a trend toward lower frequency of warfarin use among patients on enzyme-inducing AEDs, though.

Again, to identify elderly patients with newly diagnosed epilepsy, we used two data sources, a hospital register and a nationwide drug-purchase register. With the aid of the former, we could obtain detailed data on clinical characteristics and drug-based treatment of the patients. The registers of the SII have excellent coverage of outpatients' reimbursed purchases of medication that requires a prescription. Therefore, in addition to a cohort from a single hospital, we were able to gather reliable nationwide data on the use of AEDs. National prescription registries have been used previously too for identifying potential drug interactions (Johnell & Klarin 2007), also in patients with epilepsy (Gidal et al. 2009).

The risk and clinical relevance of drug interactions was assessed via the established database SFINX (Böttinger et al. 2009). Physicians' use of this database has been shown to reduce the risk of serious drug interactions in primary health care (Andersson et al. 2013). In Finland, SFINX has been integrated into the electronic medical-records and prescription systems and the physician receives automatic alerts of drug interactions when prescribing. When assessing our results, one should take into account that varying choices of AED as well as of drugs used for other conditions in different populations of elderly patients with newly diagnosed epilepsy have an impact on the overall risk of relevant interactions. Another limitation of our study is that information on patients living in nursing homes and other long-term-care facilities was not available, prompting their exclusion from our study. Treatment with AEDs is common in those populations, as is a high frequency of co-morbid conditions (Galimberti et al. 2016).

In conclusion, many elderly patients with newly diagnosed epilepsy have a high burden of co-morbidity, and they are often treated with polypharmacy. Exposure to carbamazepine is associated with possible clinically relevant pharmacokinetic interactions with drugs used

for concomitant disorders. Still, carbamazepine is well-studied and effective with elderly patients who have epilepsy, so these problems can be controlled via prediction of the possible drug–drug interactions and, if needed, more careful follow-up on the patients.

6.4 STENGTHS AND LIMITATIONS OF STUDY

Our findings are based on a community-dwelling hospital cohort and also on national register data, which should provide some guarantee as to the population-based results. Comparison of the findings between these data sources shows some differences – with regard to, for example, drug choices. The patients identified from the KUH may represent a selected group, although KUH serves as the only secondary referral center for its catchment area. Our database covering hospital patients is far more detailed than are the national register data. We were able to review the case records of the hospital patients; accordingly, the senior authors could confirm the correctness of the data. This was not possible with the data obtained from the national registers.

The study has some limitations. Identification of patients from a hospital register may be a method associated with selection bias, and the outcome was assessed retrospectively. However, the demographic and clinical characteristics of our patients seem to represent the general elderly population with epilepsy well. We also excluded patients living in nursing homes and other long-term care facilities. Treatment with AED is common in those populations as well as high frequency of co-morbid conditions (Galimberti et al. 2016). Because such patients are more disabled than community-dwelling subjects, outcome of their seizures may differ from that observed in our patients. Furthermore, Kaplan–Meier methods and multivariate analysis were employed to assess remission and predictive factors for the outcome.

6.5 SUMMARY OF THE DISCUSSION

- I First-generation AEDs are still the most commonly employed first drugs for elderly patients with newly diagnosed epilepsy in Finland. Age and comorbid conditions have an effect in the choice of the initial AED treatment.
- II The prognosis of seizures in elderly patients with newly diagnosed epilepsy is good, and most patients can be successfully treated with the first AED. Patients who do not become seizure-free within the first year are at risk of displaying a drug-resistant seizure disorder.
- III Elderly patients with newly diagnosed epilepsy are at high risk of clinically relevant pharmacokinetic interactions with other drugs, especially if exposed to carbamazepine, but these interactions can be controlled via rational drug choices and with prediction of the possible drug-to-drug interactions. Patients on dihydropyridine calcium-channel blockers, statins, warfarin, and risperidone face the highest risk of interactions.

7 Conclusions

1. First-generation AEDs are still the most commonly employed as first drugs for elderly patients with newly diagnosed epilepsy.
2. The prognosis of seizures in elderly patients with newly diagnosed epilepsy is good, and most patients can be successfully treated with the first AED.
3. Elderly patients with newly diagnosed epilepsy are at high risk of clinically relevant pharmacokinetic interactions with other drugs but these interactions can be controlled via rational drug choices and with prediction of the possible drug-to-drug interactions.

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EMMI BRUUN

This thesis aims to examine the choice of AED, outcome, and interactions with AEDs in the treatment of patients age 65 years or above with newly diagnosed epilepsy. The results show that first-generation AEDs are still the most commonly employed first drugs for elderly patients in Finland and the prognosis regarding seizure-control is good. This study demonstrated that elderly patients are at high risk of clinically relevant pharmacokinetic interactions with other drugs, especially if exposed to carbamazepine, however these interactions can be usually controlled via rational drug choices and with prediction of the possible drug-to-drug interactions.



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