



## Choice of the first anti-epileptic drug in elderly patients with newly diagnosed epilepsy: A Finnish retrospective study<sup>☆</sup>



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### ABSTRACT

**Purpose:** The choice of initial anti-epileptic drug (AED) for elderly and younger adult patients with newly diagnosed epilepsy was assessed.

**Methods:** The pattern of initial prescription of AEDs between 2000 and 2013 was retrospectively studied in two community-dwelling cohorts, identified from the case records of Kuopio University Hospital (KUH): elderly subjects (aged 65 or above at the time of diagnosis;  $n = 529$ ) and a random sample of younger adults (16–64 years old at the time of diagnosis;  $n = 201$ ). Furthermore, nationwide register data from the Social Insurance Institution of Finland were included in the analysis, from the years 2004 and 2012.

**Results:** Valproic acid (VPA) and carbamazepine (CBZ) 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 VPA and oxcarbazepine. The selection of VPA was associated with higher age ( $P < 0.001$ ), myocardial infarction ( $P = 0.003$ ), and stroke ( $P = 0.013$ ). Lower probability of receiving CBZ 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.

**Conclusion:** 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.

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## 1. Introduction

Epileptic seizures and epilepsies constitute the third most frequent neurological disorder after cerebrovascular disorders and dementing illnesses in the elderly population of both Europe and the United States [1,2]. Of all age groups, incidence rates of epilepsy are at their highest in the elderly [1–3], and the absolute number of

elderly patients with epilepsy is only going to rise further as the population continues to age [2].

The aetiology and clinical presentation of seizures in elderly patients, and possibly also the prognosis, differ from those observed in young adults. The clinical presentation of seizures may cause challenges in differential diagnosis [4]. Seizures in the elderly may be diagnosed as memory lapses or confusion, and the option of diagnosing epilepsy may be missed or diagnosis delayed [5,6]. The most common aetiologies of newly diagnosed seizures in the elderly are ischaemic stroke (with a frequency among newly diagnosed case with epilepsy of 40–50%), head injury (17%), subarachnoid haemorrhage (8–24%), and intracranial haemorrhage (8%) [7]. However, 25–40% of the newly diagnosed cases present no identifiable aetiology for the epilepsy [5]. The majority of cases of newly diagnosed epilepsy in the elderly originally manifest themselves as focal seizures [1,5].

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Most of the evidence as to the efficacy and safety of anti-epileptic drugs (AEDs) is derived from populations below 65 years of age, and randomised clinical trials in elderly patients are few in number [8–11]. In older age groups, the use and selection of AEDs may be complicated by altered pharmacokinetics and pharmacodynamics, comorbidities, polypharmacy, physiological changes, and concomitant functional impairment [7,12,13]. Furthermore, adverse effects of AEDs may qualitatively and quantitatively differ in the elderly from those seen in young adults [13]. Several sets of guidelines for the treatment of epilepsy have been published in recent years, but they give either very little or no guidance on the treatment of elderly patients [13–16]. Studies in the United States (US) have shown that, until recent years, phenytoin and other first-generation AEDs were the most commonly prescribed initial drugs in the elderly [17–19].

The primary objective of the study reported upon here was to assess the choice of first AED in community-dwelling elderly patients with newly diagnosed epilepsy in Finland. We also compared the choice of initial AED between elderly and young adults treated at the same hospital and conducted comparison with data derived from a comprehensive national drug register. Also, trends in the choice of initial AED were studied over time. Of the second-generation AEDs, oxcarbazepine (which entered use in 1991), gabapentin (1999), lamotrigine (1999), topiramate (2002), and levetiracetam (2006) have been approved for use as monotherapy in epilepsy cases. However, only oxcarbazepine is subject to full reimbursement as initial AED.

## 2. Material and methods

### 2.1. Population and setting

To assess patterns in prescription of AEDs in 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). The Finnish population (consisting of 5.4 million people in 2012) is stable and ethnically homogenous. Those aged 65 years or over number about one million.

KUH is one of five university hospitals in Finland. For epilepsy patients, it serves as a secondary centre and also a national tertiary referral centre. The population of the primary catchment area of KUH is 250,000, with around 50,000 being age 65 or above. National guidelines on the diagnosis and treatment of epilepsy recommend that all patients with suspected seizures be referred to a neurology department for evaluation [20].

#### 2.1.1. 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. Additionally, we identified seven patients in whom AED treatment was begun as polytherapy.

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.

#### 2.1.2. 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 general health insurance covering all Finnish citizens, 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 1081 incident patients met these criteria and were included in the study (see [Table 3](#)).

### 2.2. 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 [21].

The epilepsy was categorised as focal, generalised, or unclassified [22]. Epileptic seizures were classified as focal seizures, generalised seizures, or unclassified seizures.

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 [23] – were excluded.

### 2.3. Statistical analysis

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 VPA ( $n = 259$ ) or CBZ ( $n = 164$ ). It was not conducted for other AEDs, because of small sample sizes. The level for significance was determined to be  $P < 0.05$ . All statistical analyses were performed with Microsoft Excel and SPSS 19.

### 2.4. Ethical considerations

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.

### 3. Results

#### 3.1. Characteristics of the community-dwelling epilepsy-diagnosed hospital patients

In both the elderly and the young adults, there was a slight preponderance of men over women (see Table 1). 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.

#### 3.2. The choice of the first anti-epileptic drug for the hospital-group patients

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 2). The main difference was in the frequency of prescription of CBZ and VPA.

The choice of the first AED in the elderly patients varied statistically significantly ( $P < 0.001$ ) with the age group (see Fig. 1). With advancing age, the proportion of VPA increased while that of CBZ decreased.

Predictive factors for the choice of CBZ and VPA as the initial AED were analysed via binary logistic regression analysis (see Table 3). Statistically significant predictors for the choice of VPA as initial AED were myocardial infarction and ischaemic stroke or haemorrhage. Older patients were more likely to have VPA and less likely to have CBZ as their initial AED. A predictor for lower possibility of receiving CBZ as first AED was myocardial infarction, whereas diabetes and atrial fibrillation predicted a higher probability of receiving CBZ.

#### 3.3. Number and characteristics of seizures prior to treatment start in the elderly hospital-group patients

More than half of the elderly patients had experienced one or two seizures before AED treatment. There were no statistically

**Table 1**

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		Total	201	

CNS = central nervous system.

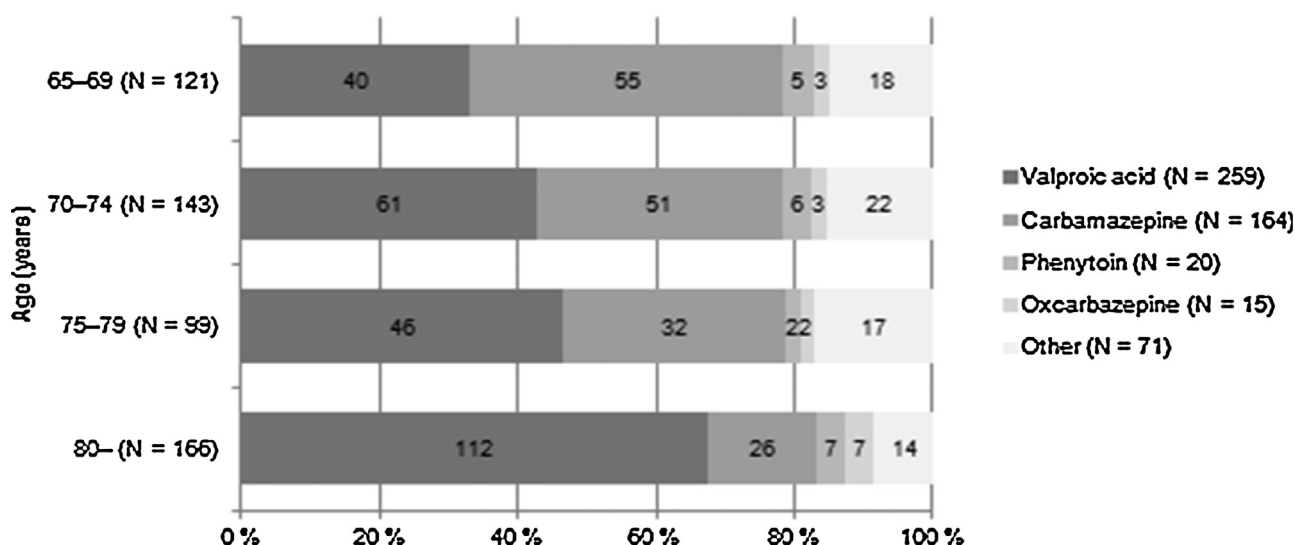
**Table 2**

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

	Elderly		Young adults	
	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	

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



**Fig. 1.** The choice of the first anti-epileptic drug, by the patient's age group.

**Table 3**

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.

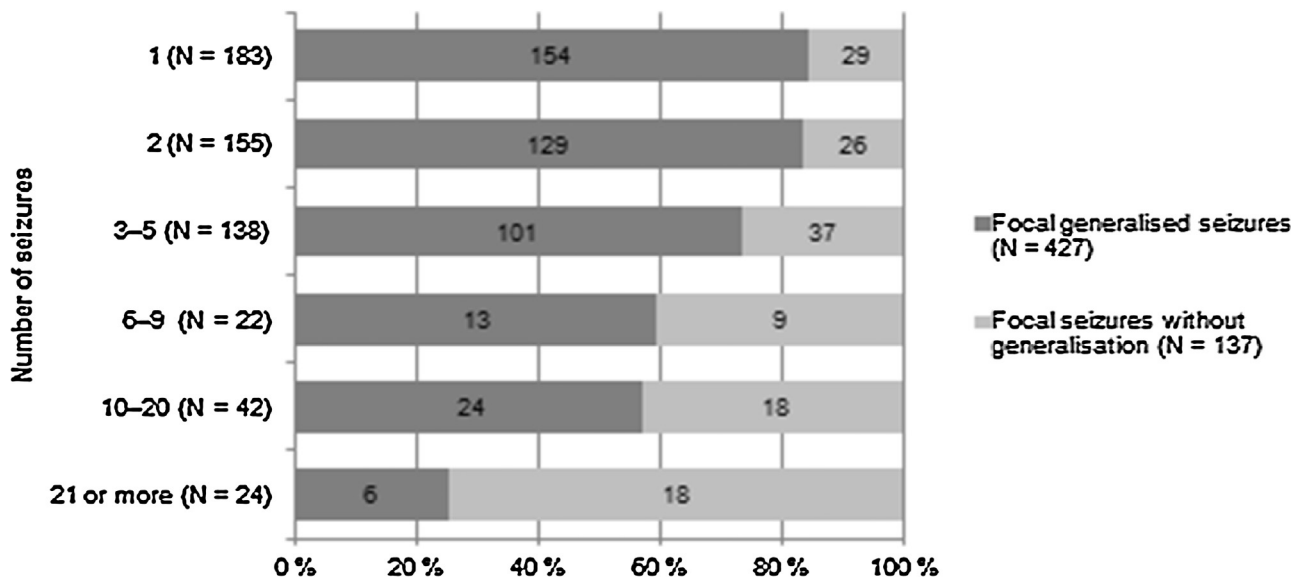


Fig. 2. The number of focal seizures prior to the start of anti-epileptic drug treatment.

focal seizures without generalisation (see Fig. 2). 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.

#### 3.4. Time trends of initial AED choices among hospital-group patients and in the whole-country register data

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 full-country dataset (see Table 4). In both hospital-patient and whole-country data, the prevalence of choice of CBZ and phenytoin as the first AED decreased and that of choosing VPA and levetiracetam increased over the span of the years examined. In the nationwide data, the use of oxcarbazepine was more frequent than it was with the hospital patients.

## 4. Discussion

According to our population-based data, VPA 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 VPA to all AEDs prescribed rose. In comparison with practices in the US [17,18], the use of phenytoin was quite limited in Finland. The Finnish guidelines on the treatment of epilepsy [20] state that, because of its adverse effects and the challenges in pharmaco-kinetics, phenytoin should not be used as primary AED for adult patients. According to the relevant guideline, VPA 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 CBZ, and good tolerability in the elderly [7,12].

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 CBZ. This frequency is twice that for the elderly. In young adults, VPA was the second most commonplace initial choice, followed by oxcarbazepine. The choices for young adults are in accordance with other studies' findings [13].

According to our study, concomitant disorders seemed to have some impact on the choice of initial AED: CBZ use was started less often in cases of patients with cardiac disorders, and VPA was favoured for patients with diagnosed myocardial infarction or stroke. In the binary logistic regression analysis, cardiac disorders

**Table 4**

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

were found to be an independent predictive factor for the choice of both CBZ and VPA. VPA has been reported to be associated with lower risk of myocardial infarction and stroke as compared with CBZ [24,25]. Because of the high prevalence of cardiovascular comorbidity in the elderly patients with epilepsy and risk of drug interactions with CBZ, VPA was favoured over CBZ in the oldest age groups. The reason for favouring of CBZ in patients with diabetes remains obscure.

Most of the new-onset seizures in the elderly have focal onset [5]. 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 [7]. 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.

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 CBZ 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 CBZ. Oxcarbazepine is more strongly associated with hyponatraemia than CBZ is [7], which may account for its lower popularity for elderly hospital-group patients. Internationally, CBZ remains one of the AEDs most commonly used for the elderly [17,26].

Pugh et al. [17,27] 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 CBZ, gabapentin, and VPA remained quite stable, but the use of levetiracetam increased. In our study, VPA and levetiracetam became more popular whilst the use of CBZ 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 [8,10,11]. 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.

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 inconsistencies – with regard to, for example, drug choices. The patients identified from the hospital may represent a selected group, although specialist evaluation at outpatient clinics is recommended by the national guidelines [20]. 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.

Management of epilepsy in the elderly requires an understanding of aetiology and pharmacological factors that are unique to older persons [5,7]. The choice of AED should be based on assessment of seizure type, concomitant medications, and co-existing 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 [7,28].

### Conflict of interest

Emmi Bruun has received support from the Finnish Epilepsy Research Foundation.

Reetta Kälviäinen has received speaker's honoraria from Eisai, UCB, and Orion; honoraria for participation in advisory boards' work from Eisai, Fenno Medical, Pfizer, and UCB; and research support for her institute from the Academy of Finland, UCB, and Eisai.

The remaining authors have no conflicts of interest. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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