Response to First Antiseizure Medication in Patients Diagnosed with Epilepsy

Running title: Response to First Antiseizure Medication

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Abstract

Objectives: To investigate the interaction among the efficacy, tolerability, and overall effectiveness of the first antiseizure medication in patients 16 years or older with newly diagnosed epilepsy.

Materials & Methods: The study included 584 patients who were referred to the Tampere University Hospital between January 1, 1995, and December 31, 2005, and were diagnosed with epilepsy. All individuals were retrospectively followed up until December 31, 2006, until reaching at least one year of seizure freedom, or until death if before the cut-off date.

Results: Overall, after thorough validation of the epilepsy diagnosis 459 patients comprised the study cohort; among these patients, 73% of males and 60% of females became seizure-free for at least one year with the first antiseizure medication. The seizure freedom rate for focal epilepsy was 67%. There was no significant difference in focal epilepsy to achieve seizure freedom between oxcarbazepine, carbamazepine or valproic acid. The seizure freedom rate among patients above 60 years of age was 67%. For patients with structural and unknown aetiology, seizure freedom rates were 61.5% and 75.3%, respectively. Additionally, epileptiform activity in EEG in patients with focal epilepsy decreased odds of seizure freedom in adjusted logistic regression models (OR 0.55, p=0.036).

Conclusions: This study provides a more positive prediction of seizure freedom compared with previous studies with the onset of epilepsy at 16 years or older with an overall estimation that two-thirds of patients with new-onset epilepsy obtain seizure freedom with the first antiseizure medication.

Keywords: antiepileptic drug, antiseizure medication, newly diagnosed epilepsy, seizure freedom, treatment outcomes.

INTRODUCTION

Epilepsy is one of the most common chronic brain disorders globally and affects people of all ages. It is estimated that approximately 0.6% of the population of Nordic countries has active epilepsy [1]. Epilepsy is still associated with stigma and psychological, social, cognitive, and economic repercussions [2].

The response to the first antiseizure medication (ASM) is the strongest predictor of long-term seizure remission [3]. The effectiveness of the first ASM in newly diagnosed patients with epilepsy has been previously studied in long-term outcome studies with seizure freedom rates below 50%, including children (older than 9 years), adolescents, adults and elderly patients with new-onset epilepsy, and these outcome measures have not improved during the past 20 years [4, 5]. In randomized controlled ASM trials and in a recent network meta-analysis in adult populations with focal epilepsy, the results are more variable, with one-year seizure-free rates ranging from 57 to 76% [6-11].

Multiple factors affect the possibility of seizure freedom in patients with newly diagnosed epilepsy, and those factors are highly dependent on the patient population studied, ASM availability, definitions applied for the diagnostic criteria of epilepsy, seizure type and epilepsy type classifications. During recent years, new International League Against Epilepsy (ILAE) official guidelines have been published on the topics of the definition of epilepsy [12], classification of seizures [13] and epilepsies [14], as well as a definition of an adequate ASM

trial in epilepsy in terms of dosage and ASM selection [15], which could enhance the comparison between different studies on seizure-free rates in people with epilepsy. However, studies utilizing these new criteria are still infrequent.

According to the new 2014 ILAE criteria, epilepsy requires at least one unprovoked seizure. The term “unprovoked” is, however, imprecise because we can never be sure that there was no provocative factor [12]. In the new ILAE classification of seizure types, a focal aware seizure (FAS) corresponds to the 1981 ILAE classification term “simple partial seizure.” A focal impaired awareness seizure (FIAS) corresponds to the prior term “complex partial seizure”. The seizure type “focal to bilateral tonic–clonic” (FBTCS) is a special seizure type, corresponding to “partial onset with secondary generalization”. FBTCS reflects a propagation pattern of a seizure rather than a unitary seizure type [13]. Of newly diagnosed focal epilepsy, 60% of patients have the FBTCS type [16].

The use of valproic acid (VPA) and carbamazepine (CBZ) has been shown to be effective in treating patients with newly diagnosed epilepsy [4]. Phenytoin (PHT) and CBZ are similar in terms of effectiveness (retention) or efficacy (seizure recurrence and seizure remission) for individuals with focal onset or generalized onset seizures [18]. Since 1994, several newer ASMs, including lamotrigine (LTG) and oxcarbazepine (OXC), have been approved by the Food and Drug Administration or European Medicines Agency [19]. OXC is a second-generation ASM with proven efficacy as monotherapy and combination therapy in the treatment of focal seizures, and it is safe to use and well tolerated in elderly patients [20].

The aim of this study was to evaluate the response to the first ASM therapy in terms of efficacy and tolerability by applying the recent ILAE criteria for i) the definition of epilepsy [11], ii) the classification of seizures [12], iii) the definition of epilepsy type and aetiology [13],

and iv) the definition of adequate ASM trial [14]. In addition, our study attempted to determine prognostic factors for seizure freedom in patients with newly diagnosed epilepsy.

MATERIALS & METHODS

Overall, 584 patients aged 16 years or older referred to the Tampere University Hospital between January 1, 1995, and December 31, 2005, were diagnosed with epilepsy. All individuals were retrospectively followed up until December 31, 2006, until reaching at least one year of seizure freedom, or until their deaths if before the cut-off date. According to the local practice guidelines, neurological patients who are at least 16 years old are treated in the adult neurology department. Medical records of the patients, including clinic visits and demographic and clinical information from the patients, were examined retrospectively. Additional studies carried out were registered. All epilepsy diagnoses were re-evaluated by a neurologist (HH) applying the new criteria for the definition of epilepsy [11]. Any ambiguities were resolved by discussions with three neurologists (HH, JS, JP) until consensus was reached.

Nearly all patients underwent at least one surface EEG performed by neurophysiologists, either using a standard approach or testing the patients after sleep deprivation. All the available original EEG reports were assessed and categorised to normal, epileptiform activity, focal slowing or unspecific findings by neurologist with special expertise in epilepsy (JP).

The clinical practice at that time favoured avoiding diagnosis of unknown epilepsy type, and all patients with no evidence of generalized epilepsy were usually diagnosed as focal epilepsy patients [21]. Neuroimaging, particularly computed tomography or magnetic resonance imaging, was performed and evaluated by neuroradiologists to screen for underlying structural

abnormalities that might have caused epilepsy. Information obtained from the history, physical examination, and other studies was used to classify the patient's epilepsy aetiology.

For all the patients who were given a diagnosis of epilepsy, ASM therapy was initiated according to standard clinical practice at that period. Subsequently, patients were followed at the epilepsy clinic according to routine clinical practice until at least one year of seizure freedom was achieved with the first ASM regimen in the present study. At the follow-up visit, clinical information and the response to ASM therapy were recorded. ASM doses were adjusted as clinical circumstances dictated, with particular attention given to efficacy and tolerability.

Depending on the variable group, comparisons were performed using the Mann-Whitney U-test, Pearson's chi-squared test, or Fisher's exact test. Binary logistic regression was used to examine the association between seizure freedom by first ASM and gender. Age at date of diagnosis (continuous), seizure type (FBTCS as a reference group), epilepsy type (focal as a reference group), ASM (OXC as a reference group) and EEG (normal as a reference) were examined as potential confounding factors. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each covariate. The data were analysed with Stata version 15.1 (College Station, TX: StataCorp LLC).

In this retrospective study, there was no contact on patients and the information was collected from patient register of Tampere University hospital. This study was approved by the Head of Tampere University Science Centre.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

RESULTS

After thorough validation of the epilepsy diagnosis, 101 patients were excluded because of uncertainty of epilepsy diagnosis or because epilepsy was not newly diagnosed. Additionally, 24 patients died within the first year after ASM therapy was initiated and were excluded for not being able to reach the end point of the one-year follow-up for the study.

Table 1 summarizes the clinical characteristics of all 459 patients with validated newly diagnosed epilepsy who remained in this study cohort. There were no significant changes in patient characteristics over the study period between therapy initiations during 1995-2000 and 2001-2005. At the time of diagnosis, the majority of the patients (260 of 459, 56.6%) were between 25 and 60 years of age. Only 20.3% (93 of 459) had their epilepsy diagnosed between 16-25 years of age and 23.1% (106 of 459) above age 60. The seizure freedom rate, defined as at least one whole year without seizures after initiation of the first ASM therapy in the whole study group, was 67.1% (308 of 459). The majority of the patients (241 of 459, 52.5%) had structural aetiology. EEG report was available of 409 (89.1%) patients.

Table 2 shows the baseline characteristics and seizure freedom outcomes by first ASM in patients with focal epilepsy. Focal epilepsy was more common among men (55.5%). The median age at diagnosis was 48, and 24.4% (106 of 434) were older than 60 years of age. In focal epilepsy, the seizure freedom rate was 66.8% (290 of 434), with significant differences related to sex, aetiology and epileptiform EEG. The seizure freedom rate was 60.1% for females and 72.2% for males ($p = 0.008$). With structural and unknown aetiology, seizure freedom rates were 61.5% and 75.3%, respectively. Seizure freedom rates for FBTCS, FAS and FIAS as the presenting seizure type were 69.4%, 66.7% and 46.2%, respectively. The seizure freedom rate

among patients above 60 years of age was 67.0%. The seizure freedom rate among patients with normal EEG in focal epilepsy was 34.6% (134 of 387).

Patients with focal epilepsy were most often prescribed OXC (280, 64.5%), followed by CBZ (77, 17.7%), VPA (47, 10.8%), PHT (14, 3.2%), and LTG (10, 2.3%) as the first ASM regimen. The seizure freedom rates for OXC, CBZ and VPA were 65.7%, 70.1% and 74.5%, respectively.

Table 3 shows the baseline characteristics and seizure freedom outcomes with the first ASM in patients with generalized epilepsy. There were no significant differences with respect to clinical characteristics. Patients with generalized epilepsy were younger than patients with focal epilepsy, with a median age of 18 years at diagnosis. The seizure freedom rate was 72.0% (18 of 25). The seizure freedom rate for females was 60.0%, and for males, it was 90.0%. Patients with generalized epilepsy were most often prescribed VPA (17 of 25, 68.0%), followed by LTG (5 of 25, 20.0%) as the first ASM regimen.

Among girls and women of childbearing age (ages 16-46 years), 12.6% (14 of 111) had VPA as the first ASM. Five had focal epilepsy, and nine had generalized epilepsy.

Table 4 provides detailed information about ORs for seizure freedom in patients with focal epilepsy with reference to sex, age at diagnosis, first ASM used, type of first seizure, aetiology and EEG. Patients with epilepsy due to an unknown aetiology had 2.2 times higher odds of seizure freedom than patients with a structural aetiology (OR 2.22, p = 0.003). In contrast, epileptiform activity in EEG decreased odds of seizure freedom (OR 0.55, p=0.036). Additionally, patients with FIAS as their presenting seizure showed tendency to less likely achieve seizure freedom than patients with FBTCS (OR 0.52, p = 0.091).

Table 5 summarizes the reasons for first ASM withdrawal in focal and generalized epilepsy and with ASM used. Furthermore, based on specific ASMs in focal epilepsy, OXC was discontinued due to side effects in 12.5% (35 of 280) of patients. Discontinuation rates due to side effects were not significantly different for other first-line ASMs, such CBZ, LTG and VPA, with rates of 14.3% (11 of 77), 20.0% (2 of 10) and 12.8% (6 of 47), respectively.

DISCUSSION

The present study, which applied the recent ILAE guidelines for the diagnosis [12] and classification of epilepsy [14], epileptic seizures [13], and definitions of an adequate ASM trial [15], provides new insights into the prognosis of newly diagnosed epilepsy. In our study, the seizure freedom rate for at least one year with the first ASM was 67% for all patients, which is higher than the 50% seizure freedom rate observed in previous studies [4, 5]. Our study provides new evidence suggesting that the prognosis of new-onset epilepsy is more granular depending on the age of the patient, aetiology and presenting seizure type, as well as the sex of the patient. Patients with focal epilepsy with unknown aetiology, normal EEG or FBTCS as the presenting seizure type have a better chance of obtaining seizure freedom than patients with structural or infectious aetiology, epileptiform activity in EEG or FIAS as the presenting seizure type.

The age distribution of patients in a given cohort does indeed have a significant effect on the total seizure-freedom outcomes because refractory epilepsy is most commonly associated with an earlier onset of epilepsy. In the landmark study by Kwan and Brodie [4] addressing the response to the first ASM therapy as a further subanalysis of the main publication [22], the mean age at onset of epilepsy in the whole study group was 32.8 years compared to 44.5 years at the

time of diagnosis in our study. Moreover, the proportion of patients with an age of diagnosis less than 25 years but 16 years or more was 20.3% (93 of 459) in our study, whereas 9.8% were between 9 and 15 years in Kwan and Brodie's study [4].

In randomized controlled trials for the first ASM monotherapy, the patients were typically adults with a mean age of approximately 40 years at the time of diagnosis [23]. In a trial in which eslicarbazepine acetate (ESL) was compared to CBZ, 71.1% of ESL–treated patients and 75.6% of CBZ–treated patients were seizure-free for ≥6 months [6]. Even though the initial 6-month response to ASMs is a valuable predictor of long-term response, the seizure freedom rate, in general, is lower when the follow-up time is longer. In a recent study, the initial 6-month seizure-freedom rate was 64%, but the 3-year seizure freedom rate declined to 46% [7]. Similarly, with lacosamide (LCM) monotherapy, the 6-month seizure freedom rate was 66% and declined to 60% at one year [8]. According to a recent meta-analysis, there were no statistical differences in the seizure freedom rates in newly diagnosed focal epilepsy between levetiracetam (LEV), zonisamide (ZNS), LCM, ESL and CBZ [11]. In another study, OXC was compared to CBZ in 235 patients aged 15–65 years with similar one-year seizure freedom rates for both ASMs (52% with OXC and 60% with CBZ) [24]. With OXC, 59% of patients with focal or generalized onset seizures have been reported to be seizure-free after one year [9]. In elderly patients with newly diagnosed epilepsy, 59% became seizure-free with the first ASM [10]. Moreover, Mohanraj and Brodie [25] reported a high responder rate for elderly patients older than 64 years, with 85% achieving at least one-year remission, although the response to the first ASM regimen for this age group was not reported separately. In a recent systematic review and meta-analysis, there were no significant differences in the seizure freedom rates in newly diagnosed elderly patients between CBZ, gabapentin (GBP), LCM, LTG, LEV, PHT and VPA

[26]. In our study, the responses in the 25-60 and more than 60 years age groups were similar in focal epilepsy. These demographic characteristics may have influenced the increased percentage of patients achieving seizure freedom in our study. Therefore, the age distribution of epilepsy patients needs to be taken into consideration when assessing the probability of seizure freedom with the first ASM.

According to our study, men with focal epilepsy were more likely to achieve seizure freedom with their first ASM than were females, but we could not identify any particular reason, including aetiology, for this unexpected finding. Underreporting is one potential explanation because a significant proportion of patients with epilepsy underreport their seizures. Forty percent of patients who anonymously reported a seizure in the past year held a driving licence, but only a quarter of these admitted to not being seizure-free [27]. Neurology's role is not only to treat epilepsy but also to regulate the rights of epileptic patients to hold a driving licence or access certain occupations. This could cause males to underreport their seizures compared to females.

In this study, we applied the new 2017 ILAE classifications of seizure and epilepsy type [13, 14]. However, none of the patients were categorized as having combined generalized and focal epilepsy, which is a new epilepsy type compared with the previous classification system, most likely due to the age distribution of our study group. In the seminal study by Kwan et al [4], epilepsies were classified into i) idiopathic, ii) cryptogenic and iii) remote symptomatic, making the comparison with the new 2017 ILAE classification ambiguous. The number of patients with generalized epilepsy was much lower in our study (5%) than in the idiopathic group (25%) in a previous study [4]. The seizure freedom rate for patients with idiopathic epilepsy was 58% [4], compared with 72% in patients with generalized epilepsy in our study. The combined seizure

freedom rate for symptomatic and cryptogenic epilepsy was 43.5% in the Kwan and Brodie study [4] compared to 67% with focal epilepsy in our study.

The new 2017 ILAE classification provides more categories based on the aetiology of epilepsy [14]. In our adult population, the vast majority fell into categories of either structural (53%) or unknown (39%) aetiology, whereas all patients with genetic aetiology (5%) were in the group of generalized epilepsy. Three percent of our patient population had infectious aetiology. In addition, none of the patients had metabolic or immune aetiology for their epilepsy since metabolic epilepsies usually begin in childhood [28] and awareness of autoimmune epilepsy increased significantly in the 2010s – over a decade after our patients were diagnosed with epilepsy [29]. Seizure freedom rates in patients with unknown aetiology were significantly higher (75%) than those in patients with structural aetiology (61%), whereas in Kwan's study, there was no difference between the patients with symptomatic (43%) and cryptogenic (44%) epilepsy. The new more granular classification of aetiologies makes the comparison between different study populations easier because the heterogeneity of different study populations with regard to age and referral system does have a substantial effect on the probabilities of achieving seizure freedom.

The major seizure types in the new 2017 ILAE classification are quite easily transferrable from the previous 1981 ILAE seizure classification [14]. In our study, FIAS as the first seizure type was associated with a trend to lower probability of seizure freedom than FBTCS and FAS. In our single-centre cohort, the proportion of patients with FIAS as their first seizure type was lower (9%) than that described in the classical incidence study from Rochester Minnesota (36%) [16]. The low proportion of FIAS may also contribute to good seizure outcomes in our study.

Epileptiform EEG has been associated with an increased risk of seizure recurrence also in previous studies [30].

Lack of efficacy (46%) and side effects (49%) were almost equally the most common reasons for the discontinuation of the first ASM. Lack of efficacy has been found to be the main reason for ASM discontinuation even with newer ASMs [5]. In our study, there were no significant differences between ASMs for the number of discontinuations, with OXC and CBZ as the most commonly used ASMs. In a previous study, OXC was compared to CBZ in 235 patients aged 15–65 years with newly diagnosed epilepsy, and the withdrawal rates due to significant adverse events were 14% with OXC and 26% with CBZ [24]. In a previous study from Finland, 3-year retention rates with OXC and CBZ were similar (72.7% and 79.6%, respectively) [31]. In a recent network meta-analysis discontinuation rates due to side-effects for different ASMs were also between 11-19% [11]. Treatment with CBZ was associated with a higher risk of discontinuation than that with LTG, LEV, or VPA in the elderly [24].

Due to the retrospective study design, selection bias is a potential limitation of this study. In addition, our cohort consisted of patients from an era when newer ASMs were not yet widely used or existed. However, due to the reimbursement policy, CBZ, OXC and VPA are currently chosen as first-line ASMs for focal epilepsy in Finland. Nevertheless, the new ASMs have not yet improved the probabilities of seizure freedom [5, 11, 24]. Due to our study design, an initial seizure freedom rate of at least one year was used, but long-term seizure freedom rates were not available. We were unable to document a possible underreporting of seizures. The low proportion of FIAS in our cohort may also be due to the lack of recognition of these seizures that has been previously described [32].

CONCLUSIONS

Our study provides new data for the prediction of seizure freedom in the adult population with the onset of epilepsy at 16 years or older, providing a more positive outlook compared with previous studies with an overall estimation that two-thirds of patients with new-onset epilepsy already obtain seizure freedom with the first ASM use. Additionally, favourable prognostic factors include male sex, unknown aetiology, no epileptiform activity in EEG or FBTCS or FAS as the presenting seizure type. Furthermore, only 12.0% of the patients discontinued their first ASM due to side effects.

REFERENCES

[1] Syvertsen M, Koht J, Nakken KO. Prevalence and incidence of epilepsy in the Nordic countries. *Tidsskr Nor Laegeforen* 2015;**135**(18):1641-1645.

[2] Fisher RS, van Emde Boas W, Blume W, *et al*. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;**46**(4):470-472.

[3] Mohanraj R, Brodie MJ. Early predictors of outcome in newly diagnosed epilepsy. *Seizure* 2013;**22**(5):333-344.

[4] Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia* 2001;**42**(10):1255-1260.

[5] Chen Z, Brodie MJ, Liew D, *et al*. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. *JAMA Neurol* 2018;**75**(3):279-286.

[6] Trinka E, Ben-Menachem E, Kowacs PA, *et al*. Efficacy and safety of eslicarbazepine acetate versus controlled-release carbamazepine monotherapy in newly diagnosed epilepsy: A phase III double-blind, randomized, parallel-group, multicenter study. *Epilepsia* 2018;**59**(2):479-491.

[7] Xia L, Ou S, Pan S. Initial Response to Antiepileptic Drugs in Patients with Newly Diagnosed Epilepsy As a Predictor of Long-term Outcome. *Front Neurol* 2017;**8**:658.

[8] Villanueva V, Giraldez BG, Toledo M, *et al.* Lacosamide monotherapy in clinical practice: A retrospective chart review. *Acta Neurol Scand* 2018;**138**(3):186-194.

[9] Bill PA, Vigonius U, Pohlmann H, *et al.* A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. *Epilepsy Res* 1997;**27**(3):195-204.

[10] Bruun E, Kalviainen R, Keranen T. Outcome of initial antiepileptic drug treatment in elderly patients with newly diagnosed epilepsy. *Epilepsy Res* 2016;**127**:60-65.

[11] Lattanzi S, Zaccara G, Giovannelli F, et al, Antiepileptic monotherapy in newly diagnosed focal epilepsy. A network meta-analysis. *Acta Neurol Scand* 2019. Jan;139(1):33-41.

[12] Fisher RS et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014;**55**(4):475-82.

[13] Fisher RS, Cross JH, French JA, *et al.* Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;**58**(4):522-530.

[14] Scheffer IE, Berkovic S, Capovilla G, *et al.* ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;**58**(4):512-521.

[15] Kwan P, Arzimanoglou A, Berg AT, *et al.* Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;**51**(6):1069-1077.

[16] Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia* 1993;**34**(3):453-468.

[17] Marini C, King MA, Archer JS, *et al.* Idiopathic generalised epilepsy of adult onset: clinical syndromes and genetics. *J Neurol Neurosurg Psychiatry* 2003;**74**(2):192-196.

[18] Nevitt SJ, Marson AG, Tudur Smith C. Carbamazepine versus phenytoin monotherapy for epilepsy: an individual participant data review. *Cochrane Database Syst Rev* 2019;**7**:CD001911.

[19] St Louis EK. Truly "rational" polytherapy: maximizing efficacy and minimizing drug interactions, drug load, and adverse effects. *Curr Neuropharmacol* 2009;**7**(2):96-105.

[20] Kutluay E, McCague K, D'Souza J, *et al.* Safety and tolerability of oxcarbazepine in elderly patients with epilepsy. *Epilepsy Behav* 2003;**4**(2):175-180.

[21] Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1989;**30**(4):389-399.

[22] Early identification of refractory epilepsy. Kwan P, Brodie MJ. *N Engl J Med*. 2000 Feb 3;342(5):314-9.

[23] Kim JH, Lee SK, Loesch C, *et al*. Comparison of levetiracetam and oxcarbazepine monotherapy among Korean patients with newly diagnosed focal epilepsy: A long-term, randomized, open-label trial. *Epilepsia* 2017;**58**(4):e70-e74.

[24] Dam M, Ekberg R, Loyning Y, *et al*. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. *Epilepsy Res* 1989;**3**(1):70-76.

[25] Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. *Eur J Neurol* 2006;**13**(3):277-282.

[26] Lattanzi S, Trinka E, Del Giovane C, et al. Antiepileptic drug monotherapy for epilepsy in the elderly: A systematic review and network meta-analysis. Epilepsia. 2019 Nov;60(11):2245-2254.

[27] Dalrymple J, Appleby J. Cross sectional study of reporting of epileptic seizures to general practitioners. *BMJ* 2000;**320**(7227):94-97.

[28] Lin Lin Lee V, Kar Meng Choo B, Chung YS, *et al*. Treatment, Therapy and Management of Metabolic Epilepsy: A Systematic Review. *Int J Mol Sci* 2018;**19**(3):10.3390/ijms19030871.

[29] Toledano M, Pittock SJ. Autoimmune Epilepsy. *Semin Neurol* 2015;**35**(3):245-258.

[30] Berg AT. Risk of recurrence after a first unprovoked seizure. *Epilepsia.* 2008;**49** Suppl 1:13-8.

[31] Rainesalo S, Peltola J, Auvinen A, *et al*. Retention rate of oxcarbazepine monotherapy in an unselected population of adult epileptics. *Seizure* 2005;**14**(1):72-74.

[32] Beghi E. The Epidemiology of Epilepsy. *Neuroepidemiology* 2020;**54**(2):185-191.

Table 1. Background characteristics (median and interquartile range or frequency and percentage) at the last clinic visit for all patients divided by the year when first antiseizure medication treatment was initiated

	All patients	1995-2000	2001-2005
N	459	239	220
Sex, n (%)			
Female	208 (45.3)	109 (45.6)	99 (45.0)
Male	251 (54.7)	130 (54.4)	121 (55.0)
Duration of follow-up, years, med (IQR)	2.6 (4.0)	4.2 (5.7)	1.8 (2.3)
Age at date of diagnosis, med (IQR)	45.0 (31.0)	43.0 (29.0)	48.0 (34.5)
Aetiology, n (%)			
Structural			
Benign tumour	19 (4.1)	11 (4.6)	8 (3.6)
Hippocampal sclerosis	3 (0.7)	2 (0.8)	1 (0.5)
Malformation of cortical development	11 (2.4)	5 (2.1)	6 (2.7)
Malignant tumour	21 (4.6)	9 (3.8)	12 (5.5)
Other hippocampal pathology	12 (2.6)	5 (2.1)	7 (3.2)
Perinatal injury	5 (1.1)	5 (2.1)	0
Traumatic brain injury	27 (5.9)	15 (6.3)	12 (5.5)
Vascular lesion	113 (24.6)	61 (25.5)	52 (23.6)
Vascular malformation	30 (6.5)	9 (3.8)	21 (9.5)
Genetic	25 (5.4)	14 (5.9)	11 (5.0)
Infectious	15 (3.3)	9 (3.8)	6 (2.7)
Unknown	178 (38.8)	94 (39.3)	84 (38.2)
Epilepsy type, n (%)			
Focal	434 (94.6)	225 (94.1)	209 (95.0)
Generalized	25 (5.4)	14 (5.9)	11 (5.0)
Type of first seizure, n (%)			
FBTCS	320 (69.7)	172 (72.0)	148 (67.3)
FAS	75 (16.3)	37 (15.5)	38 (17.3)
FIAS	40 (8.7)	16 (6.7)	24 (10.9)
GTCS	15 (3.3)	10 (4.2)	5 (2.3)
Myoclonic	9 (2.0)	4 (1.7)	5 (2.3)
EEG			

Normal	188 (41.0)	94 (39.3)	94 (42.7)
Epileptiform activity	103 (22.4)	60 (25.1)	43 (19.5)
Focal slowing	66 (14.4)	38 (15.9)	28 (12.7)
Unspecific	52 (11.3)	25 (10.5)	27 (12.3)
No EEG	50 (10.9)	22 (9.2)	28 (12.7)
First antiseizure medication			
Carbamazepine	78 (17)	60 (25.1)	18 (8.2)
Clonazepam	2 (0.4)	1 (0.4)	1 (0.5)
Gabapentin	1 (0.2)	0 (0)	1 (0.5)
Lamotrigine	15 (3.3)	9 (3.8)	6 (2.7)
Levetiracetam	1 (0.2)	0 (0)	1 (0.5)
Oxcarbazepine	281 (61.2)	136 (56.9)	145 (65.9)
Phenobarbital	1 (0.2)	1 (0.4)	0 (0)
Phenytoin	14 (3.1)	10 (4.2)	4 (1.8)
Tiagabine	1 (0.2)	1 (0.4)	0 (0)
Topiramate	1 (0.2)	0 (0)	1 (0.5)
Valproic acid	64 (13.9)	21 (8.8)	43 (19.5)

FAS = focal aware seizure; FBTCS = focal to bilateral tonic-clonic seizures; FIAS = focal impaired awareness seizure; GTCS = generalized tonic-clonic seizures, IQR = interquartile range, med = median, n = number.

Oliko todella että näillä kaikilla jolla oli no EEG todella no EEG vai no EEG report available

Table 2. Baseline characteristics (median and interquartile range or frequency and percentage) at the last clinic visit in categories of seizure freedom by first antiseizure medication for patients with focal epilepsy

	Seizure freedom by first ASM		
	Yes	No	*p*
N	290	144	
Sex, n (%)			0.008[1]
Female	116 (40.0)	77 (53.5)	
Male	174 (60.0)	67 (46.5)	
Duration of follow-up, years, med (IQR)	1.9 (2.9)	4.2 (4.2)	<0.001[2]
Age at date of diagnosis, med (IQR)	47.5 (29.0)	48.0 (31.5)	0.90[2]
Aetiology, n (%)			0.049[3]
Structural			
Benign tumour	10 (3.4)	9 (6.3)	
Hippocampal sclerosis	1 (0.3)	2 (1.4)	
Malformation of cortical development	5 (1.7)	6 (4.2)	
Malignant tumour	10 (3.4)	11 (7.6)	
Other hippocampal	8 (2.8)	4 (2.8)	
Perinatal	4 (1.4)	1 (0.7)	
Traumatic brain injury	19 (6.6)	8 (5.6)	
Vascular lesion	69 (23.8)	44 (30.6)	
Vascular malformation	21 (7.2)	9 (6.3)	
Infectious	9 (3.1)	6 (4.2)	
Unknown	134 (46.2)	44 (30.6)	
Type of first seizure, n (%)			0.015[1]
FBTCS	222 (76.6)	98 (68.0)	
FAS	50 (17.2)	25 (17.4)	
FIAS	18 (6.2)	21 (14.6)	
EEG *			0.0421
Normal	134 (46.2)	48 (33.3)	
Epileptiform activity	50 (17.2)	39 (27.1)	
Focal slowing	46 (15.9)	20 (13.9)	
Unspecific	32 (11.0)	18 (12.5)	
No EEG	28 (9.7)	19 (13.2)	

ASM = antiseizure medication; FBTCS = focal to bilateral tonic-clonic seizures; FAS = focal aware seizures; FIAS = focal impaired awareness seizures, IQR = interquartile range, med = median, n = number.

[1] Pearson's chi-squared test; [2] Mann-Whitney U-test

Table 3. Baseline characteristics (median and interquartile range or frequency and percentage) at the last clinic visit in categories of seizure freedom by first antiseizure medication for patients with generalized epilepsy

	Seizure freedom by first ASM		
	Yes	No	*p*
N	18	7	
Sex, n (%)			0.18[1]
Female	9 (50.0)	6 (85.7)	
Male	9 (50.0)	1 (14.3)	
Duration of follow-up in year, med (IQR)	2.8 (5.0)	4.3 (6.7)	0.15[2]
Age at date of diagnosis, med (IQR)	19.0 (7.0)	18.0 (3.9)	0.57[2]
Type of first seizure, n (%)			0.21[1]
GTCS	13 (72.2)	3 (42.9)	
Myoclonic	5 (27.8)	4 (57.1)	
EEG *			0.33[1]
Normal	3 (18.8)	3 (50.0)	
Epileptiform activity	11 (68.8)	3 (50.0)	
Unspecific	2 (12.5)	0	

ASM = antiseizure medication; GTCS = generalized tonic-clonic seizures, IQR = interquartile range, med = median, n = number.

[1] Fisher's exact test; [2] Mann-Whitney U-test; * No EEG for three patients (yes 2, no 1)

Table 4. Odds ratios with their 95% confidence intervals and p-values from unadjusted and adjusted logistic regression models for seizure freedom in patients with focal epilepsy

	OR (95% CI)	*p*	OR (95% CI)	*p*
Gender (ref. = female)	1.70 (1.11 to 2.61)	0.016	1.78 (1.12 to 2.81)	0.014
Age at date of diagnosis			1.01 (0.99 to 1.02)	0.25
First ASM (ref. = Oxcarbazepine)				
Carbamazepine			1.20 (0.65 to 2.22)	0.56
Valproic acid			1.68 (0.71 to 3.98)	0.24
Lamotrigine			0.67 (0.17 to 2.56)	0.56
Phenytoin			0.80 (0.23 to 2.80)	0.73
Other ASM			0.39 (0.06 to 2.47)	0.32
Type of first seizure (ref. = FBTCS)				
FAS			1.08 (0.58 to 1.99)	0.81
FIAS			0.52 (0.25 to 1.11)	0.091
Aetiology (ref. = Structural)				
Infectious			0.86 (0.24 to 3.09)	0.82
Unknown			2.22 (1.32 to 3.72)	0.003
EEG (ref. = Normal)				
Epileptiform activity			0.55 (0.31 to 0.96)	0.036
Focal slowing			1.04 (0.54 to 2.01)	0.91
Unspecific			0.79 (0.39 to 1.59)	0.51

ASM = antiseizure medication; CI = confidence interval; FAS = focal aware seizures; FBTCS = focal to bilateral tonic-clonic seizures; FIAS = focal impaired awareness seizures; OR = odds ratio; ref = reference.

Table 5. Reasons for the withdrawal of the first antiseizure medication (frequency and percent)

	Reason for the withdrawal		
	Lack of efficacy	Side effects	Other reasons
Epilepsy type			
Focal	49 (46.2)	54 (50.9)	3 (2.8)
Generalized	2 (40.0)	3 (60.0)	0
Total	51 (45.9)	57 (51.4)	3 (2.7)
Antiseizure medication			
Carbamazepine	8 (40.0)	12 (60.0)	0
Clonazepam	1 (100)	0	0
Lamotrigine	1 (25.0)	3 (75.0)	0
Oxcarbazepine	31 (44.9)	37 (53.6)	1 (1.4)
Phenobarbital	1 (100)	0	0
Phenytoin	3 (60.0)	0	2 (40.0)
Tiagabine	0	1 (100)	0
Valproic acid	6 (60.0)	4 (40.0)	0