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Predictors of remission in patients with epilepsy

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ABSTRACT

Aim of study. To evaluate the rate and factors predicting seizure remission in a large cohort of patients with epilepsy.

Materials and methods. Patients with epilepsy treated at a university epilepsy clinic were included in this study. The following information was collected by means of a structured questionnaire: age, sex, age at onset of epilepsy, aetiology of epilepsy, the presence of intellectual disability, duration and type of epilepsy, frequency of seizures, treatment of epilepsy, and mechanism of action of antiepileptic drugs (AEDs).

Results. A total of 530 adult patients participated in this study (mean age ± standard deviation: 36.1 ± 12.6 years). Of these, 327 (61.7%) were female, and 364 (68.7%) patients had focal epilepsy. Twelve-month seizure freedom was achieved in 246 (46.4%) patients. Logistic regression revealed several independent predictors of seizure freedom: younger age (odds ratio (OR) = 0.98; p = 0.037), male sex (OR = 1.54; p = 0.050), generalised epilepsy (OR = 1.61; p = 0.052), lower number of prescribed AEDs (OR = 0.22; p = 0.001), and taking a combination of valproate and lamotrigine (OR = 2.51; p = 0.024).

Conclusions. Most patients with epilepsy enter remission on monotherapy with their first or second AED. However, a substantial proportion of patients may benefit from combination therapy including valproate and lamotrigine polytherapy.

Key words: epilepsy, remission, polytherapy, monotherapy, mechanism of action

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Introduction

Epilepsy, with a prevalence of active disease of 6.38 per 1,000 persons, is one of the most common neurological disorders [1]. Although nondrug therapies such as surgery, implantable devices, or a ketogenic diet are highly effective in some cases, for the vast majority of patients antiepileptic drugs (AEDs) are the mainstay of treatment. Currently used AEDs suppress the occurrence of seizures; however, they do not possess antiepileptogenic or disease-modifying activity. As a result, patients with epilepsy require long-term, or even lifelong, treatment with AEDs. Despite the development and introduction of many new AEDs with a differing mechanism of action (MOA) over the last two decades, the probability of achieving seizure freedom has not significantly increased [2, 3].

The correct classification of the type of seizure/epilepsy and the syndrome is indispensable for the appropriate management and prognosis. The International League Against Epilepsy (ILAE) recently released two position papers of its Commission for Classification and Terminology. These papers facilitate the classification of seizures and epilepsies, and therefore the choice of an adequate AED [4, 5]. Geographical and socioeconomic factors (i.e. specific aetiologies of epilepsy, ethnicity, availability of AEDs, and access to specialised epilepsy centres) can influence the outcome of epilepsy. Thus, each group of the population should have its own data on the treatment and outcome of epilepsy. Taking these points into consideration, we decided to study the treatment outcome in a large cohort of Polish adult patients with epilepsy.

Materials and methods

This was a retrospective study. Patients with epilepsy who were seen at the university epilepsy outpatient clinic between 1 January, 2015 and 31 December, 2019 were identified from the electronic database. We included patients who were seen by one of the authors (MB) with a minimum period of observation and treatment of 12 months, and who had at least three

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visits during the study period. Epilepsy was diagnosed according to the ILAE's practical clinical definition of epilepsy [6]. The following information was collected by means of a structured questionnaire: age, sex, age at onset of epilepsy, aetiology of epilepsy, duration and type of epilepsy, frequency of seizures, the presence of intellectual disability, AEDs treatment, and the MOA of the AEDs. Seizure types were classified according to the position paper of the ILAE's Commission for Classification and Terminology [5]. Epilepsies were divided into four types: focal, generalised, combined (generalised and focal), and unknown. The aetiology of epilepsy was categorised as structural/infectious, genetic or presumed genetic, or unknown [4].

The exclusion criteria were as follows: (a) no pharmacological treatment for epilepsy; (b) underlying progressive neurological or systemic disorder (mainly neoplasms); (c) coexistence of psychogenic nonepileptic seizures; and (d) non-drug treatment i.e. epilepsy surgery, deep brain stimulation, or vagus nerve stimulation. Seizure freedom was defined as a patient experiencing no seizures in the past ≥ 12 months [7].

The study protocol was approved by the university's bioethical committee, and the protocol of the study followed the principles of the Helsinki Declaration.

Statistical analysis

Firstly, we assessed the distribution of variables using the Kolmogorov–Smirnov test and checked the skewness and kurtosis, assuming that values < –2 or > 2 conform to a normal distribution [8]. Then, we analysed the sociodemographic and clinical data with Student's *t*-test or Mann–Whitney *U* test (depending on the distribution), as well as with chi-square test (in case of frequencies). Finally, for testing the causal inferences between the dependent (patients' remission) and independent variables, we built a multiple logistic regression model with selected potential factors affecting the patients' state, adjusted for sex and age. All criteria were met and the model's goodness of fit was analysed with the Hosmer-Lemeshow test. Calculations were performed using the Statistica 13.1 package. The level of statistical significance was determined at $p < 0.05$.

Results

530 adult patients were included in this study (mean age ± standard deviation (SD): 36.1 ± 12.6 years; range: 18–84). Of these, 327 (61.7%) were female, and 364 (68.7%) had focal epilepsy. The average age at the onset of epilepsy was 18.6 ± 13.1 years. Twelve-month seizure freedom was achieved in 246 (46.4%) patients. A definite cause of epilepsy was identified in 53.4% of the cases, with structural/infectious aetiology being the most common. In 80 (15.1 %) patients, intellectual disability was found. Table 1 sets out the clinical characteristics of the study group regarding age, sex, age at onset of epilepsy, type and aetiology of epilepsy, frequency of seizures, the number of currently used AEDs, and its dosage. More than half of the patients (292, 55.1%) were on monotherapy; the most commonly used AEDs were levetiracetam, valproate (VPA), and lamotrigine (LTG).

Table 1. General characteristics of studied patients with epilepsy and current treatment of epilepsy

Variable	
Female sex; n (%)	327 (61.7%)
Age (years) mean (± SD) [range]	36.1 (± 12.6) [18–84]
Age at onset of epilepsy (years); mean (± SD) [range]	18.6 (± 13.1) [1–72]
Duration of epilepsy (years); mean (± SD) [range]	17.4 (± 11.7) [1–58]
Aetiology of epilepsy	
Genetic/presumed genetic	128 (24.1%)
Structural/infectious	155 (29.3%)
Unknown	247 (46.6%)
Type of epilepsy type; n (%)	
Generalised	126 (23.8%)
Focal	364 (68.7%)
Combined (generalised and focal)	15 (2.8%)
Unknown	25 (4.7%)
Frequency of seizures; n (%)	
Remission	246 (46.4%)
No remission	284 (53.6%)
Intellectual disability	80 (15.1%)
Number of currently used AEDs; mean (range)	1.6 (1–5)
Monotherapy; n (%)	292 (55.1%)
Polytherapy; n (%)	238 (44.9%)
Number of drug trials	
Mean (±SD) [range]	3.4 (± 2.5) [1–17]
Median	3
The most commonly used AEDs (in mono- or polytherapy); n (%) and its mean daily dose (mg/day) [range]	
Levetiracetam	234 (44.1%) 1,992 [500–4,500]
Valproic acid	215 (40.6 %) 1,378 [500–4,000]
Lamotrigine	147 (27.7%) 301 [50–700]
Carbamazepine	72 (13.6%) 981 [200–3,600]
Topiramate	54 (10.2%) 270 [50–600]

AEDs — antiepileptic drugs; SD — standard deviation

A large majority (173, 72.7%) of the patients undergoing combination therapy were treated with two AEDs; 58 (24.4%) and seven (2.9%) patients were treated with three and

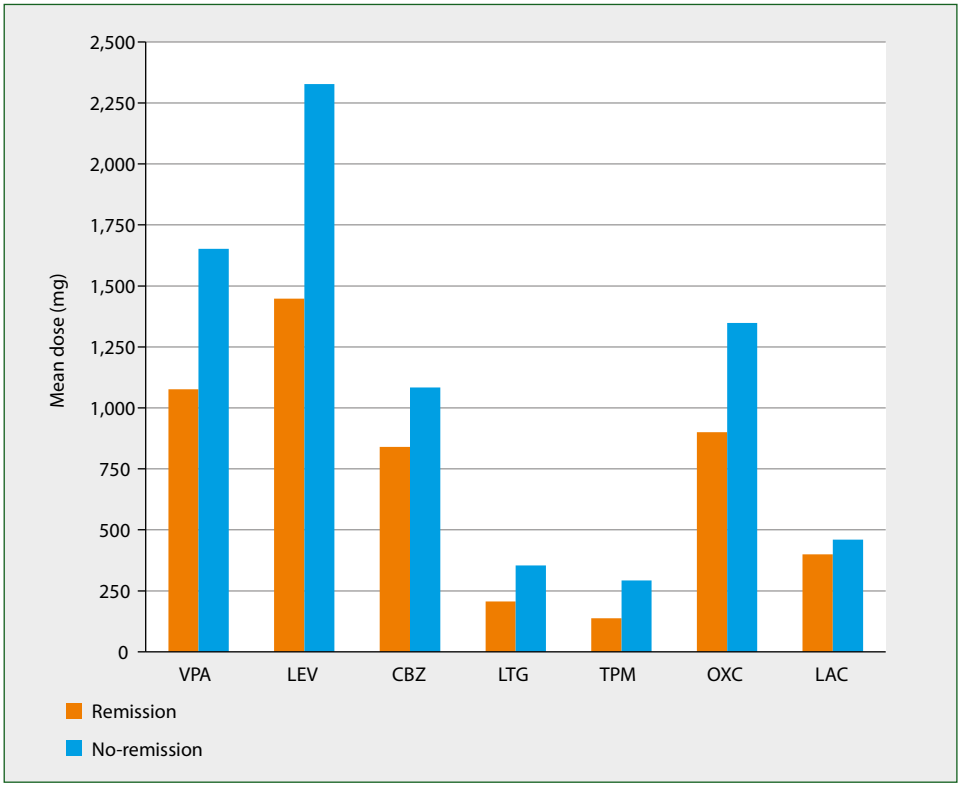

Figure 1. Mean daily doses of antiepileptic drugs in patients with remission and persistent seizures. VPA — valproate; LEV — levetiracetam; CBZ — carbamazepine; LTG — lamotrigine; TPM — topiramate; OXC — oxcarbazepine; LAC — lacosamide

≥ 4 drugs, respectively. 228 (95.8%) patients on polytherapy were prescribed AEDs with differing MOAs, and 55 (23.1%) patients took a combination of VPA and LTG. Among the seizure-free patients, 191 (77.6%) took one AED. Of the 65 patients on ≥ 3 drugs, only five (7.7%) achieved 12-month remission. Patients with persistent seizures were prescribed higher mean doses of AEDs than those in remission (Fig. 1).

We included into univariate analysis age, gender, age at onset of epilepsy, aetiology of epilepsy, type of epilepsy, the presence of intellectual disability, AEDs treatment (mono- *vs* polytherapy), number of currently used AEDs, number of AEDs' trials, and treatment with a VPA+ LTG combination. Due to multicolinearity with the type of epilepsy, we excluded aetiology of epilepsy from further analysis.

Table 2 sets out a comparison of clinical features and treatment parameters in patients in remission and in patients with persistent seizures. Seizure-free patients were younger, had a shorter duration of epilepsy, more frequently were on monotherapy, and suffered from generalised epilepsy. Intellectual disability was less frequent in seizure-free patients. The number of prescribed AEDs and the number of previously tried AEDs was lower in this group.

Multivariate analysis revealed several independent predictors of seizure freedom: younger age (odds ratio (OR) = 0.98; 95% confidence interval (95%CI) = 0.95–0.99; p = 0.037), male sex (OR = 1.54; 95%CI = 1.00–2.40; p = 0.050), generalised epilepsy (OR = 1.61; 95%CI = 1.00–2.56; p = 0.052), lower number of prescribed AEDs (OR = 0.22; 95%CI = 0.10–0.47; p = 0.001), and taking a combination of VPA and LTG (OR = 2,51; 95%CI = 1.11–5.55; p = 0.024). The model explains 28% of dependent variable's variance and achieves a good fit.

Discussion

In a large cohort of patients treated at the university epilepsy clinic, the overall rate of 12-month seizure freedom was 46.4%. This percentage is much lower than that reported in the recently published longitudinal observational cohort study by Chen et al., where the rate of remission in patients with newly diagnosed epilepsy was as high as 63.7% [3]. This discrepancy may be partly explained by the fact that the majority of the patients treated in our clinic were referred by general practitioners or neurologists due to refractory epilepsy or AED-related side effects.

In logistic regression analysis, we found several independent predictors of seizure freedom: younger age, male sex, generalised epilepsy, lower number of prescribed AEDs, and taking a combination of VPA and LTG.

In our study, similar to the study of Mäkinen et al., older age was associated negatively with remission [9]. This result may reflect the permanent pharmacoresistance of epilepsy. Male patients and subjects with generalised epilepsy had a higher probability of seizure freedom. These findings are

Table 2. Clinical characteristics of patients in remission compared to patients with persistent seizures

	Remission (N = 246)		No-remission (N = 284)		
	n	%	n	%	P-value
Gender					
Female	154	62.6	173	60.9	$\chi^2 = 0.16$ P = 0.690
Male	92	37.4	111	39.1	
Epilepsy type					
Generalised	77	31.3	49	17.3	$\chi^2 = 28.71$[a]
Focal	151	61.4	213	75	P < 0.001
Combined (generalised and focal)	1	0.4	14	4.9	
Unknown	17	6.9	8	2.8	
Presence of intellectual disability	25	10.2	55	19.4	$\chi^2 = 8.71$ P = 0.003
AEDs therapy					
Monotherapy	191	77.6	101	35.6	$\chi^2 = 85.85$ P < 0.001
Polytherapy	55	22.4	183	64.4	
MOA in patients on polytherapy					
Different	55	100	173	94.5	$\chi^2 = 1.88$ P = 0.171
SCB	0	0	10	5.5	
VPA+LTG					
Yes	15	6	30	11	$\chi^2 = 3.38$ P = 0.066
No	231	94	254	89	
	Mean (± SD)	Median	Mean (± SD)	Median	
Age (years)	34.1 (± 12.2)	31	37.9 (± 12.7)	36	T = –3.58 P < 0.001
Age at onset of epilepsy (years)	19.2 (± 12.7)	17	18.1 (± 13.5)	16	T = 0.88 P = 0.379
Duration of epilepsy (years)	14.7 (± 10.1)	13	19.7 (± 12.5)	18	T = –5.10 P < 0.001
Number of AEDs	1 (± 0.5)	1	1.9 (± 0.8)	2	Z = –10.28 P < 0.001
AED's trial number	2.3 (± 1.47)	2	4.4 (± 2.7)	4	Z = –10.50 P < 0.001

[a] Generalised epilepsy was more frequent in patients with remission (P < 0.001); focal and combined generalised and focal epilepsy were more frequent in patients without remission (P < 0.001). AEDs — antiepileptic drugs; MOA — mechanism of action; SCB — sodium channel blocker; SD — standard deviation

concordant with the results of Chen et al. [3]. The higher percentage of seizure-free males may be related to the decreasing usage of highly effective AEDs with teratogenic potential, such as VPA or topiramate, in women. Patients with generalised epilepsy were more likely to enter remission. Moreover, most patients with generalised epilepsy and persistent seizures had less disabling types of seizures, including myoclonic or absence. Genetic generalised epilepsies typically respond well to treatment [10, 11]. The probability of remission decreased substantially with the higher number of currently used and previously tried AEDs, which is in line with the results of previous studies [3, 12, 13]. Nevertheless, seizure freedom on polytherapy was achieved by a substantial proportion of patients (55; 22.4%), which is consistent with the findings of Stephen et al. [14].

Combining drugs with different MOAs is thought to be more successful in patients requiring polytherapy, although the clinical evidence in support of this strategy is very limited [15]. The clinical efficacy of pharmacodynamic synergism of VPA/LTG polytherapy was proved by Brodie and Yuen [16]. With regards to MOA, the vast majority (95.8%) of the patients on polytherapy were prescribed AEDs with a different MOA. This made a comparison of the efficacy of rational polytherapy with combining AEDs with the same MOA impossible. However, we found that the combination of VPA and LTG was an independent predictor of remission. This AED combination appears to have synergistic therapeutic effects due to both pharmacokinetic and pharmacodynamic interactions [15–18]. In clinical practice, the concomitant use of VPA and LTG may pose a therapeutic challenge due to significant

pharmacokinetic interactions and the risk of LTG-related skin rash. VPA as a potent inhibitor of UDP-glucuronosyltransferase inhibits LTG metabolism with a marked prolongation of LTG half-life and a reduction of LTG dosage requirements in patients co-medicated with VPA. LTG administration may be associated with idiosyncratic skin and systemic adverse reactions, which are more frequent with fast increments in LTG dosage. The introduction of LTG in patients co-medicated with VPA should be undertaken with caution, using a lower starting dose and a slower pace of escalation [17, 18].

The mean doses for AEDs used in refractory patients were higher than those in seizure-free patients, a fact which poses a considerable risk of overtreatment in terms of unnecessary doses and side effects [19]. According to Mohanraj and Brodie, the majority of patients achieve remission with modest or moderate daily doses, which accords with the results of our study [20].

Our study has some limitations. Firstly, we defined remission as no seizures in the past ≥ 12 months [7]. However, patients may enter early or late remission, on or off medication. Early remission is not always followed by a lasting seizure-free period. Moreover, there are many prognostic factors of treatment response, such as aetiology, number of seizures at diagnosis, seizures during sleep, epileptiform abnormalities, abnormalities on neuroimaging, psychiatric comorbidity, medication adherence, and previous episodes of status epilepticus, which we were not able to evaluate due to small sample size or lack of information [21–27].

Secondly, the studied cohort involved a limited sample size of adult patients followed up in the university epilepsy clinic; these may differ substantially from the general population of patients with epilepsy with regard to the frequency of seizures or use of polytherapy. Thirdly, this was a retrospective study and therefore some information may have been missed. Finally, many newer AEDs, such as eslicarbazepine, brivaracetam, perampanel, and zonisamide are not available or are not reimbursed in Poland, which makes comparisons to other studies more difficult.

Conclusions

The majority of patients with epilepsy achieve seizure freedom on monotherapy, and with their first or second AED. However, one in five patients may benefit from polytherapy. Thus, we hypothesise that a combination therapy comprising VPA and LTG may prove useful in pharmacoresistant cases.

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