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Retention rate of first antiepileptic drug in poststroke epilepsy: A nationwide study

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ABSTRACT

Purpose: To describe the retention rates of first antiepileptic drugs (AEDs) in patients with poststroke epilepsy on a nationwide scale.
Methods: The Swedish Stroke Register, which has 94% coverage and high-resolution data on stroke, comorbidities, and disability, was cross-referenced to the National Patient Register, Drug Register, and Cause-of-Death Register. Patients with onset of AED-treated epilepsy after stroke in 2005–2010 were included. An algorithm based on prescription renewal intervals was used to analyze treatment data until the end of 2014.
Results: A total of 4991 patients were included. First AEDs analyzed were carbamazepine (n = 2373), valproic acid (n = 943), levetiracetam (n = 555), lamotrigine (n = 519), phenytoin (n = 176), and oxcarbazepine (n = 89). The five-year retention rate was highest for lamotrigine (75%, 95%CI:70.4–79.4), followed by levetiracetam (69%, 95%CI:62.9–74.3), oxcarbazepine (68%, 95%CI:55.2–79.8), valproic acid (62%, 95%CI:57.8–66.4), carbamazepine (60%, 95%CI:57.6–62.4), and phenytoin (55%, 95%CI:45.2–64.0). There were minor differences in baseline characteristics with low levels of disability being slightly more common in patients treated with lamotrigine and levetiracetam. Atrial fibrillation and hypertension were more common in patients treated with levetiracetam, and atrial fibrillation was less common in patients treated with carbamazepine. In a Cox model adjusted for baseline characteristics, the risk of discontinuation was lower for lamotrigine (HR 0.53, 95%CI:0.43-0.67) and levetiracetam (HR 0.75, 95%CI:0.60-0.94) when compared to carbamazepine.
Conclusions: Lamotrigine and levetiracetam have higher retention rates than carbamazepine in poststroke epilepsy. This is in agreement with existing small RCTs in this patient group.

1. Introduction

Stroke causes 14–21% of epilepsy and is the leading cause of epilepsy after middle age [1]. Poststroke epilepsy (PSE) complicates at least 6% of infarctions and 12% of ICH, respectively [2–4]. Specific evidence to guide treatment of PSE is surprisingly scarce. Carbamazepine has been a traditional choice in focal epilepsy, but concerns that elderly patients may be vulnerable to side effects, and that induction of liver enzymes may interfere with secondary stroke prophylaxis, has led to an interest in other AEDs in PSE [5,6]. Two small, open-label RCTs have demonstrated better short-term tolerability of lamotrigine and levetiracetam than slow-release carbamazepine in patients with PSE [7,8]. Observational uncontrolled single-center studies have also found good tolerability of levetiracetam and gabapentin, but little long-term data exist [9–11]. Interestingly, a recent network meta-analysis of the two RCTs suggests that side effects are less likely to occur with lamotrigine than levetiracetam [12].

We performed a nation-wide investigation of retention rates of the first AED in patients with PSE, using cross-referenced national registers and algorithmic analysis of prescription data. Our research question was if other AEDs demonstrated higher long-term retention rates than carbamazepine, as suggested by the RCTs.

2. Material and methods

2.1. Study design and study cohort

This was a retrospective cohort study based on nation-wide registers. The cohort was selected from patients registered in the Swedish Stroke Register (Riksstroke) between 2005–2010, based on information

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on epilepsy in the National Patient Register (NPR) and antiepileptic drugs in the Drug Register (DR). The Riksstroke output contained 131,330 unique individuals. We excluded patients who had a prior seizure-related diagnosis (ICD-10: G40, G41, and R56.8, ICD-9: 345 and 780C, n = 4063), died during the first two months after stroke (n = 21,697), or had registration anomalies (age > 110 or < 18, death before stroke, or incomplete date of death, n = 65). Poststroke epilepsy was defined as previously described; patients with an epilepsy-related diagnosis (ICD-10 G40, G41 or R56.8) registered at least seven days after the date of the index stroke (to avoid acute symptomatic seizures) [2]. For the purpose of the present analysis, we included all patients with a first-ever dispensation of an AED (ATC-code N03 A) after their epilepsy diagnosis (n = 4991).

2.2. Registers, clinical data and prescription analyses

The country-wide Swedish Stroke Register was established in 1994 [13], and all hospitals admitting acute stroke patients participate in the registry (http://www.riksstroke.org/eng/). The Swedish Stroke Register has an estimated coverage of 94% for acute stroke in adults and includes information on living conditions, comorbidities prior to stroke, medical treatment, rehabilitation, and support, including follow-up data at three months. The data from the Swedish Stroke Register was cross-linked with data from NPR, DR, and CDR [14]. The NPR contains information on all diagnoses registered at inpatient care from 1987 and hospital-based outpatient care since 2001 (with improved coverage in 2005). The validity of the epilepsy diagnosis G40 in NPR is approximately 90% [15]. We also included R568 and G41, since the possibility of an epilepsy diagnosis already after one late poststroke seizure was not established practice in the study period although many patients may have received treatment in this clinical scenario. The DR includes information on all prescribed drugs dispensed at a pharmacy in Sweden, and the CDR contains mortality data for all Swedish inhabitants. Transfer of prescription data to the DR is automatic and reporting to the CDR is mandatory. NPR was the source of information on epilepsy-related diagnoses, DR was the source of information on AED dispensations, and CDR contributed with dates of death. Patients were followed until death or end of study on Dec 31, 2014.

Treatment start was defined as the first dispensation date of an AED. Continued treatment required at least two dispensations per year, and treatment end was defined as more than one year without renewal. Patients with dispensations of a second AED within one week of the first were categorized as combination. Time of treatment end was defined as three months after the last AED dispensation since the standard prescription renewal interval in Sweden is three months. Hypertension, atrial fibrillation, and diabetes were defined as an occurrence of each diagnosis in either NPR or the Swedish Stroke Register. Statin treatment was defined as multiple dispensations of statins in the DR before the epilepsy diagnosis.

2.3. Ethical approval

This study, performed in agreement with privacy legislation in Sweden, was approved by the regional ethics committee in Gothenburg (approval number 187-15). The National Board of Health and Welfare anonymized all data after linkage and before we were given access to them. Patients are informed that registration in the Swedish Stroke Register is voluntary.

2.4. Statistical analyses

Frequencies and Kaplan Meier analyses were computed in SPSS version 23. Cox regression models were calculated in SAS version 9.4. Mean and standard deviations are reported for continuous variables and median and range for categorical variables. Fishers exact test was used for comparison of binary proportions, and Chi-square test was used for step-wise increasing strata. For Kaplan Meier (KM) and Cox analyses, time was calculated from treatment start to treatment end (event), with censoring at death or 31/12/2014. The unadjusted Cox model and KM analyses were based on 4986 patients since five patients had a date of death prior to their first AED dispensation. The retention rate was calculated using survival tables and 95%CI as 196 x standard error. First AED was the only covariate in the unadjusted Cox model, and background characteristics were additional covariates in the adjusted Cox model. Missing data were considered as such, and no imputations were made. All statistical tests were two-sided with alpha = 0.05.

2.5. Data availability statement

All relevant data are reported within the paper. The underlying Swedish national registers are not readily available, but protected by Swedish laws on privacy and health care confidentiality.

3. Results

3.1. Baseline characteristics and treatment pattern

The most commonly prescribed AED was carbamazepine (n = 2373), followed by valproic acid (n = 943), levetiracetam (n = 555), lamotrigine (n = 519), and phenytoin (n = 176). We also analyzed oxcarbazepine (n = 89). Remaining patients (n = 336) were prescribed AEDs used by less than 20 patients (topiramate, phenobarbital, clonazepam), AEDs frequently used for other indications (pregabalin or gabapentin), or two or more AEDs in combination.

The baseline characteristics of the 4991 patients in the cohort, including demographics, stroke type, and disability, are presented in Table 1. Differences were small between patients prescribed different first AEDs, but unassisted mobility at the three month follow-up was slightly more common in patients treated with levetiracetam or lamotrigine, and need for assistance was more common in patients given valproic acid. Atrial fibrillation, hypertension, and statin treatment were more common in patients who were treated with levetiracetam. Atrial fibrillation was less frequent in patients who were treated with carbamazepine.

During the study period, carbamazepine was replaced by levetiracetam as the most commonly prescribed first AED (Fig. 1). Patients that were prescribed a second AED were most often prescribed levetiracetam if they had started with any other first AEDs. Patients that were prescribed a second AED after levetiracetam were most often prescribed lamotrigine.

3.2. Retention rate

We used KM curves to analyze retention rates (Fig. 2). The five-year retention-rate was highest for lamotrigine (75%, 95%CI:70.4–79.4%), followed by levetiracetam (69%, 95%CI:62.9–74.3%), oxcarbazepine (68%, 95%CI:55.2–79.8%), valproic acid (62%, 95%CI:57.8–66.4%), carbamazepine (60%, 95%CI:57.6–62.4%), and phenytoin (55%, 95%CI:45.2–64.0%).

3.3. Risk of discontinuation

Finally, Cox proportional hazard models were used to assess the risk of treatment end, with carbamazepine as reference (Table 2). In an unadjusted model, the risk of treatment end was significantly lower for lamotrigine, levetiracetam, and valproic acid. In a model adjusted for the baseline characteristics presented in Table 1 and year of AED start based on 4114 patients with complete data sets, lamotrigine and levetiracetam had significantly lower risks of discontinuation.

Table 1
Baseline characteristics for all patients and the five most commonly prescribed first AEDs; CBZ = carbamazepine, VPA = valproic acid, LEV = levetiracetam, LTG = lamotrigine, and PHT = phenytoin, plus OXC = oxcarbazepine. HT = hypertension. Living category 'other' includes nursing home. Characteristics significantly different from patients with other AEDs are indicated by asterisks; * = $p < 0.05$, ** = $p < 0.01$, *** $p < 0.001$.

	All n = 4991	CBZ n = 2373	VPA n = 943	LEV n = 555	LTG n = 519	PHT n = 176	OXC n = 89
Age AED start (mean, SD)	74 (12)	73 (13)***	76 (11)***	74 (12)	73 (14)	76 (11)**	74 (11)
Sex	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Male	2732 (55)	1350 (57)	509 (54)	306 (55)	253 (49)	99 (56)	55 (62)
Female	2259 (45)	1023 (43)**	434 (46)	249 (45)	266 (51)**	77 (44)	34 (38)
Stroke type							
ICH	839 (17)	450 (19)	128 (14)	85 (15)	72 (14)	33 (19)	13 (15)
Infarction	4152 (83)	1923 (81)***	815 (86)**	470 (85)	447 (86)	143 (81)	76 (85)
Assist mobility at stroke onset							
None	4675 (94)	2248 (95)	869 (93)	534 (97)	478 (93)	159 (92)	86 (97)
Outdoors	189 (4)	81 (3)	42 (5)	12 (2)	27 (5)	9 (5)	1 (1)
Indoors/bed	99 (2)	37 (2)*	23 (3)	5 (1)*	12 (2)	5 (3)	2 (2)
Missing	28	7	9	4	2	3	0
Assist mobility 3 months							
None	2388 (57)	1140 (57)	416 (55)	309 (66)	274 (61)	73 (53)	40 (56)
Outdoors	791 (19)	385 (19)	166 (22)	72 (16)	78 (17)	33 (24)	10 (14)
Indoors/bed	986 (24)	485 (24)	182 (24)	85 (18)***	97 (22)	31 (23)	22 (31)
Missing	826	363	179	89	70	39	17
Living at stroke onset							
Unassisted	4263 (86)	2062 (87)	776 (83)	480 (87)	448 (87)	137 (79)	80 (90)
Assist at home	520 (11)	226 (10)	113 (12)	61 (11)	50 (10)	26 (15)	5 (6)
Other	181 (4)	76 (3)*	44 (5)*	11 (2)	20 (4)	11 (6)*	4 (5)
Missing	27	9	10	3	1	2	0
Living 3 months							
Unassisted	2072 (49)	1002 (49)	341 (44)	271 (57)	252 (56)	61 (42)	32 (44)
Assist at home	1025 (24)	466 (23)	231 (30)	106 (23)	87 (19)	47 (32)	18 (25)
Other	1123 (27)	561 (28)	206 (27)***	95 (20)***	114 (25)**	37 (26)	23 (32)
Missing	771	344	165	83	66	31	16
Clinical characteristics							
HT	3300 (66)	1534 (65)*	640 (68)	392 (71)*	337 (65)	117 (67)	53 (60)
Atrial fib.	1712 (34)	745 (31)***	330 (35)	240 (43)***	182 (35)	59 (34)	32 (36)
Diabetes	986 (20)	472 (20)	174 (19)	116 (21)	103 (20)	31 (18)	20 (23)
Statins	2765 (55)	1271 (54)*	501 (53)	388 (70)***	308 (59)	74 (42)***	45 (51)

3.4. Sensitivity analysis

The results were similar if our definition of combination treatment was altered to include only simultaneously dispensed AEDs.

4. Discussion

We present findings from the largest observational study on AED treatment in PSE to date. Our results in more than 4900 patients show that lamotrigine and levetiracetam have higher retention rates than carbamazepine. This is in agreement with observations from small RCTs and indicates that lamotrigine or levetiracetam may be good first treatment options in PSE. Importantly, morbidity and mortality after stroke make RCTs vulnerable to selection bias, for referral reasons and fear of low completion rates. A major advantage of our approach is the nationwide scope, minimizing these sources of bias. As expected, the patients in our material were older (average age 74 vs 67 and 69–74) [7,8] and had higher NIHSS scores (mean 9 vs 5/6.8) [8] than patients in the RCTs. Register-based investigations do not provide detail, but our findings support the real-life validity of the RCT results.

Some of our findings merit special attention. Overall, carbamazepine was the most commonly prescribed initial AED, followed by

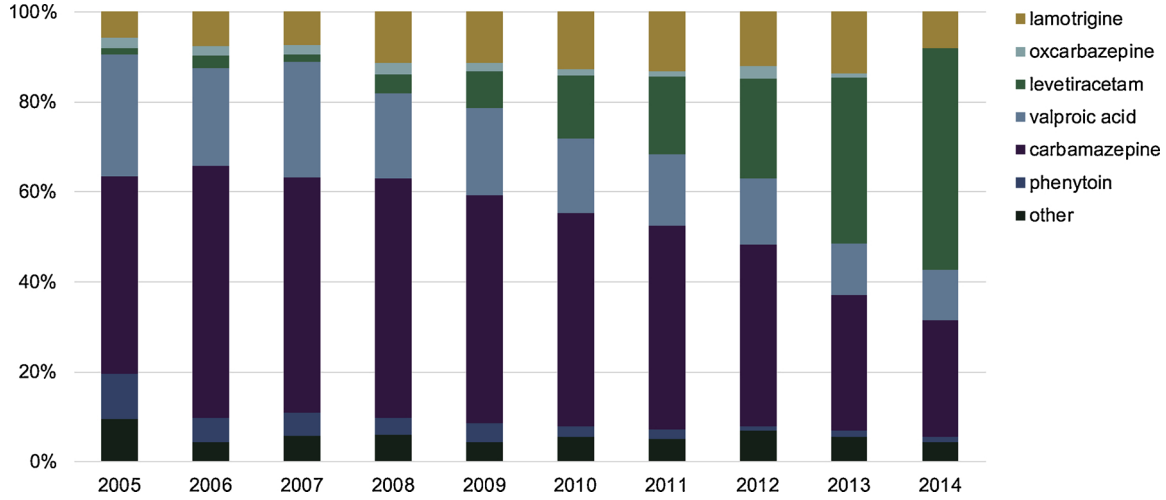

Fig. 1. Treatment pattern. Proportions of first AEDs during the study period.

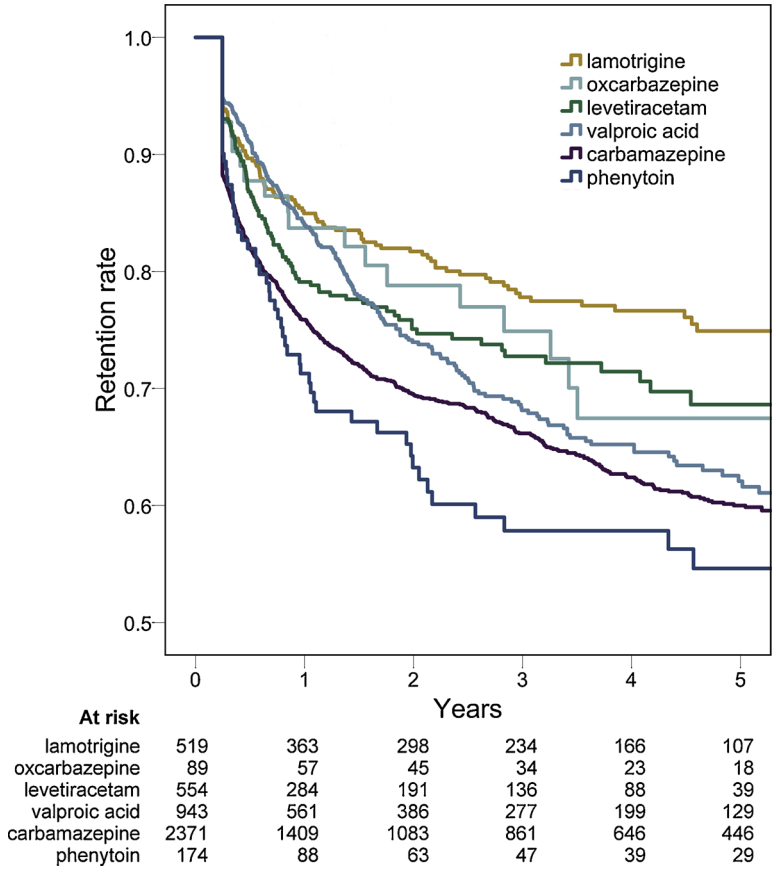

Fig. 2. Retention rates. Kaplan Meier curves illustrating discontinuation of the first AED.

Table 2
Risk of discontinuation of the first AED in Cox models, crude and adjusted for baseline characteristics. CBZ = carbamazepine, VPA = valproic acid, LEV = levetiracetam, LTG = lamotrigine, PHT = phenytoin, OXD = oxcarbazepine.

	Crude (n = 4986)		Adjusted (n = 4114)	
	HR	95%CI	HR	95%CI
CBZ	ref		ref	
VPA	0.82	0.71-0.95	0.88	0.75-1.03
LEV	0.77	0.64-0.94	0.75	0.60-0.94
LTG	0.56	0.45-0.69	0.53	0.43-0.67
PHT	1.18	0.90-1.54	1.14	0.84-1.54
OXC	0.74	0.48-1.13	0.90	0.57-1.40

valproic acid. Internationally, both drugs are used regularly among elderly patients with epilepsy [16,17]. In the end of the study period, levetiracetam replaced carbamazepine as the most commonly used first AED. This is an interesting finding, since patients who were prescribed phenytoin or carbamazepine had a higher risk of treatment discontinuation compared to patients treated with non-enzyme-inducing AEDs. The altered prescription pattern might reflect increased awareness of the drawbacks of enzyme-induction and the fact that levetiracetam is easy to titrate and devoid of drug interactions. Another finding that supports this theory is the higher prevalence of atrial fibrillation in patients treated with levetiracetam compared to carbamazepine and phenytoin, possibly suggesting some awareness of the interactions between enzyme-inducers and anticoagulants. This awareness may vary across the medical community, since high use of enzyme-inducers has been found in other stroke patient cohorts [18].

However, lamotrigine had the lowest rate of discontinuation of all AEDs in our material. In the RCT comparing lamotrigine to carbamazepine in PSE, lamotrigine had very low rates of discontinuation due to side effects. [8] Similar results were seen in the RCT on levetiracetam, which had fewer side effects than carbamazepine [7]. The five-year retention rates were not significantly different between lamotrigine and levetiracetam in our material. Nonetheless, our findings support the notion of lamotrigine being a well-tolerated AED in PSE, although the slow titration rate required might limit its usefulness in patients in acute seizure situations. The finding is in agreement with other studies on epilepsy in the elderly, in which cerebrovascular disease was a prominent etiology [19,20].

Our study has the limitations normally associated with register-based investigations. We used retention rate, an integrated measure of tolerability and efficacy not able to discriminate between the two. Withdrawal may, therefore, be due to poor seizure control and/or side effects. The relative sharp decline in retention rate during the first year for phenytoin might reflect its role in acute treatment of status epilepticus. For the same reasons, we may have underestimated the retention rate of levetiracetam and valproic acid slightly. However, this should not affect our main findings since carbamazepine and lamotrigine are not utilized in the same way. In addition, we decided to use a conservative definition of discontinuation, allowing patients a full year to renew prescriptions. This minimizes the impact of shorter disturbances, for instance, travel or longer hospitalizations, but may have underestimated withdrawal rates slightly. We will not have identified if a patient stopped using one AED, tried another, and then returned to the first. This is, however, relatively rare in epilepsy practice. Finally, our last data is from 2014 and we could therefore not capture newer AEDs. A repeat survey in a few years may shed light on the retention rates of lacosamide and other newer AEDs. Although we have tried to correct for baseline characteristics, residual confounding is a possibility in that physicians may have selected AEDs for reasons not captured by the baseline characteristics.

The main strength of our study is the use of comprehensive nationwide registers, allowing us to use the high-resolution data in the Swedish Stroke Register to adjust for stroke severity and comorbidities. The results regarding oxcarbazepine should be interpreted with caution, given the low number of patients.

Patients with PSE constitute a large epilepsy patient group. We have recently demonstrated that PSE is associated with increased mortality also with adjustment for stroke severity [2]. This is a cause for concern. Seizure-associated risks are not sufficient to explain the increased risk of death, and judging from death certificates, most patients with PSE die from vascular disease [21]. Our interpretation is that patients with PSE may be a cardiovascular high-risk group, which should be taken into account when treating PSE. Among possible measures is choosing non-enzyme-inducing AEDs which do not interfere with stroke prophylaxis or AEDs with low risks of side-effects that may hamper the ability of patients to heed lifestyle advice. Our findings that patients with PSE are most likely to continue with lamotrigine and levetiracetam indicate that these drugs may be good first treatment options.

A critical question is whether AED choice has an impact on prognosis, most importantly mortality. Interactions with stroke prophylaxis aside, some AEDs may cause atherogenic serum lipid profiles and have been suggested to increase the risk of cardiac death [22–24]. The impact of these theoretical risks in patients with PSE has not been investigated. AED side effects could also hamper stroke rehabilitation [25]. We will in future studies attempt to analyze if the choice of AED affects the risk of death or stroke recurrence.

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