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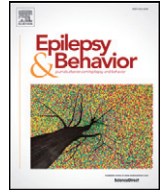
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Medication use in poststroke epilepsy: A descriptive study on switching of antiepileptic drug treatment[☆]

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ABSTRACT

Objective: Currently, as evidence-based guidelines are lacking, in patients with poststroke epilepsy (PSE), the choice of the first antiepileptic drug (AED) is left over to shared decision by the treating physician and patient. Although, it is not uncommon that patients with PSE subsequently switch their first prescribed AED to another AED, reasons for those switches are not reported yet. In the present study, we therefore assessed the reasons for switching the first prescribed AED in patients with PSE.

Method: We gathered a hospital-based case series of 53 adult patients with poststroke epilepsy and assessed the use of AEDs, comedication, and the reasons for switches between AEDs during treatment. We also determined the daily drug dose (DDD) at the switching moment.

Results: During a median follow-up of 62 months (Interquartile range [IQR] 69 months), 21 patients (40%) switched their first prescribed AED. Seven patients switched AED at least once because of ineffectivity only or a combination of ineffectivity and side effects, whereas 14 patients switched AED at least once because of side effects only. The DDD was significantly ($p < 0.001$) higher in case of medication switches due to ineffectivity (median 1.20, IQR 0.33) compared to switching due to side effects (median 0.67, IQR 0.07). There was no difference in the use of comedication between the group that switched because of ineffectivity compared to the group that switched because of side effects.

Conclusion: In our case series, up to 40% of patients with epilepsy after stroke needed to switch their first prescribed AED, mostly because of side effects in lower dosage ranges.

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1. Introduction

Stroke is the cause of about 10% of all epilepsy and 55% of newly diagnosed seizures among the elderly [1]. Nevertheless, there are no specific evidence-based guidelines regarding treatment of patients with poststroke epilepsy (PSE). Therefore, the choice of antiepileptic drug

(AED) is left over to shared decision by the treating physician and patient. From the 2013 International League Against Epilepsy (ILAE) report on initial monotherapy for epileptic seizures and syndromes, it appears that carbamazepine, levetiracetam, phenytoin, and zonisamide have 'level A' evidence for treating focal epilepsy in adults [2–5]. This may already guide the choice of the AED by mainly effectivity arguments. On the other hand, according to a recent study by Larsson et al., in patients with PSE, retention rates are highest for levetiracetam and lamotrigine, and lowest for carbamazepine and phenytoin [6], meaning that carbamazepine and phenytoin are more often switched to another drug or discontinued. A 2018 review of randomized controlled trials on AED for the treatment of PSE found that levetiracetam and lamotrigine were better tolerated than carbamazepine [7]. However, reasons for

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discontinuation or switching of AEDs in patients with PSE are not reported. We therefore aimed to study the reasons for switching the first prescribed AED in patients with epilepsy after stroke.

2. Patients and methods

We prospectively gathered a case series of 53 adult patients with seizures after stroke, by screening consecutive patients visiting the outpatient clinic of the department of Neurology at the Maastricht University Medical Center because of PSE, and including all eligible patients willing to participate in an observational study. Eligible patients had to have had at least one poststroke seizure, for which AED treatment was started. Seizures were defined by the treating neurologist using the ILAE criteria for generalized seizures (e.g., bilateral uncontrolled movements, tonic posture, and/or loss of consciousness) and focal seizures (i.e., hallucinations, and motor or sensory symptoms with evidence of seizure progression) [8]. The cutoff point between early-onset poststroke seizures (ES) and late-onset poststroke seizures (LS) was seven days [9]. Poststroke epilepsy was defined as the occurrence of one or more LS after a clinically overt stroke (with normal brain imaging or imaging showing a cerebral infarction or primary intracerebral hemorrhage), or after a clinically occult cerebral infarction detected on brain imaging during work up because of a seizure.

Retrospectively, we assessed, using the electronic patient files, the infarct/hemorrhage characteristics on CT or magnetic resonance imaging (MRI) scan, or the clinical stroke syndrome when imaging showed no abnormalities, previous and current AED use and comedication (especially psychotropic drugs because of the interactions with AEDs that could occur). Switching of medication was defined as discontinuation of one AED and starting of another AED; switches in dosage of the same AED were not considered switches in medication. We also determined the defined daily dose (DDD) at the switching moment [10].

2.1. Statistical analysis

All statistical analyses were performed using SPSS Statistics 25 (IBM, Armonk, NY, USA). Results are expressed as median \pm interquartile range (IQR) unless otherwise specified. Differences in the DDD between AED switches related to ineffectivity and AED switches related to side effects were evaluated using the nonparametric Mann–Whitney *U* test. Statistical tests were two-tailed and *p*-values < 0.05 were considered significant.

2.2. Ethical statement

The local Medical Ethical Committee gave permission for this study, and the study was conducted in accordance with the Helsinki declaration. All patients who participated in this study provided written informed consent.

3. Results

We included 53 patients with seizures after stroke in our study. From these, 4 patients had ES only (these did actually not qualify for the PSE diagnosis, but still were treated with AEDs and therefore included in the analysis); 9 patients had ES and LS, and 41 only had LS. Of these, 5 patients had an occult brain infarct detected during work up (brain imaging) because of a seizure. The median time from clinical stroke to first seizure was 8 months (IQR 19), and the median follow-up after PSE diagnosis was 62 months (IQR 69). Characteristics of the strokes are shown in Table 1.

Regarding treatment, choices for the first prescribed AED and reasons for switching this AED are shown in Table 2. In total, 32 of 53 patients (60%) retained their first prescribed AED during the complete follow-up period. In the 7 patients that switched AED at least once because of recurrent seizures only or recurrent seizures in combination

Table 1
Baseline characteristics and characteristics of stroke.

Female sex – n (%)	17 (32%)
Age at stroke – years (mean/standard deviation)	59 \pm 13.0
Infarction – n	45
Cortical – n	40
Middle cerebral artery – n	35
Anterior cerebral artery – n	2
Posterior cerebral artery – n	3
Lacunar – n	4
Brainstem – n	1
Hemorrhage – n	8

with side effects (later referred to as switch due to ineffectivity), a total of 11 switches in AED could be assessed for analyzing the DDD. In the 14 patients that switched AED at least once because of side effects only, a total of 14 switches in AED could be assessed for analyzing the DDD. The DDD was significantly higher in case of medication switches due to ineffectivity (median 1.20, IQR 0.33) compared to the DDD in case of medication switches due to side effects (median 0.67, IQR 0.07; *p* < 0.001). There were no differences in comedication between the two groups, especially not for the use of psychotropic medication: 6 of the 14 (43%) patients that switched medication because of side effects used psychotropic drugs compared to 3 of the 7 (43%) patients that switched medication because of ineffectivity. Furthermore, in general, we found no differences in age nor in number of drugs used besides AED in the group of patients that switched AED because of side effects compared to the group of patients that did not switch medication. The median age in case of AED switches due to side effects was 68 years (IQR 20), compared to the median age of 69 years (IQR 18) in case of no AED switch. The median number of drugs used besides AED in case of AED switches due to side effects was 6 (IQR 5), compared to the median number of 7 drugs uses besides AED (IQR 5) in case of no AED switch.

The side effects which related to switching from carbamazepine were malaise (in 2 patients), drug-related exanthema (in 2 patients), memory complaints, hair loss, hyponatremia, nausea, and liver function impairment. For levetiracetam these side effects were excessive sleepiness (in 2 patients), mood complaints (in 2 patients), insomnia, liver function impairment, and itching sensations. For valproic acid, side effects were myalgias, insomnia, excessive sleepiness, tremor, and increase of tremor (in a patient with Parkinson's disease); and for phenytoin, drowsiness due to intoxication (in 5 patients).

4. Discussion

In our case series of 53 PSE patients, we found that, during a median follow-up of 62 months (IQR 69 months), 21 patients (40%) switched the AED that was first prescribed, whereas 32 patients (60%) continued using the first prescribed AED. Seven patients switched AED at least once because of ineffectivity only or a combination of ineffectivity and side effects, whereas 14 patients switched AED at least once because of side effects only. The DDD was significantly higher in case of medication switches due to ineffectivity compared to switches due to side effects. To our knowledge, this is the first study to describe the reasons for switching AED in PSE to date, while confirming the retention rates in patients with PSE between 55 and 75% in a recent nation-wide register-based study [6].

Because of the interactions between AEDs and psychotropic drugs, possibly also pharmacodynamically concerning the side effects, we expected more psychotropic drugs to be used in the group of patients that switched medication due to side effects; however, we found no difference in comedication between the two groups. Similarly, we did not find effects of older age or number of concomitant drugs on switching. Nevertheless, 40% of patients switched the first prescribed AED, indicating that these patients did experience side-effects or a lack of effectivity

Table 2

First AED started and reasons for switching. For patients on carbamazepine median age was 69 years and median follow-up of 84 months, for patients on levetiracetam 62.5 years and 51.5 months of follow-up, for phenytoin 73 years and 39 months of follow-up, and for valproic acid 74 years and 38 months of follow-up.

	All patients (N = 53)	Patients on carbamazepine (N = 24)	Patients on levetiracetam (N = 14)	Patients on phenytoin (N = 10)	Patients on valproic acid (N = 5)
Patients retaining the AED first prescribed					
Age: 69 years (median)	32 (60%)	14 (58%)	11 (79%)	5 (50%)	2 (40%)
Follow-up: 61.5 months (median)					
Patients that switched the first AED					
Age: 62 years (median)	21 (40%)	10 (42%)	3 (21%)	5 (50%)	3 (60%)
Follow-up: 63 months (median)					
Reason for switching the first AED					
Ineffectivity	5	4	–	–	1
Side effects	14	6	3	5	–
Both	2	–	–	–	2

of the AED indicating that PSE might not be as well-controlled by drugs, or AED may not be tolerated as well as was described in a previous paper by Ferlazzo et al. [11]. Guidelines, like the 2013 ILAE report [2], might change tolerability and efficacy, as recommendations are made from previous trials in patients with PSE; however, most of the AED used in patients in our study already belong to the recommended AEDs in that report. Possibly, newer AEDs will perform better, as also suggested by Larsson et al. [6], with e.g., a 75% retention rate for lacosamide.

Our findings give some important insights in the use of AED in PSE; however, our study has some limitations. First, the small study population and the retrospective data assessment of the study limits the possibility of statistical analyses, as subgroups of patients using particular AEDs are too small. Second, as we included patients with the diagnoses some time ago, most of our patients were treated with older generation AEDs. A study on patients with more recent diagnoses might deliver more information on the newer AEDs. Despite these limitations, we meticulously tried to determine the reason for switching AEDs, leading to one of the first reports in its kind to our knowledge on retention of AEDs, specifically in patients with PSE, with an explicit statement on the reasons for switching.

In conclusion, up to 40% of patients with epilepsy after stroke needed to switch their first prescribed AED, mostly because of side effects in lower dosage ranges. Choosing the right AED treatment is therefore important, and newer AEDs with lower side-effect rates might do better in patients with PSE.

Declaration of Competing Interest

No author reported a conflict of interest.

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