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Attitudes towards the switching of anti-epileptic medications in pharmacies: the patients' perspective

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Abstract

Purpose: A survey of epilepsy patients' experiences of and attitudes towards the pharmacy switching of anti-epileptic medications.

Methods: A structured questionnaire was administered to a group of epilepsy patients treated at the Institute of Psychiatry and Neurology and the Medical University of Silesia, Poland. Two hundred and eleven patients (mean [± SD] age: 41.0 ± 15.6 years) were recruited; 60.6% were women. 68.2% had been treated for over 10 years.

Results: Most individuals (63%) claimed that they had never bought a generic substitute medication. Among the patients who declared that a switch had been proposed to them at a pharmacy (~40%), only 68.7% received any explanation at all from a pharmacist. Some reported positive emotions mostly related to a lower price of the new drug but also to the explanations received. Most respondents who accepted the pharmacy switch (67.4%) did not notice any significant changes in the efficacy or tolerability of treatment, while the remaining subjects reported an increase in seizure frequency (23.2%) and deterioration in treatment tolerance (9%).

Conclusions: Around 40% of Polish epilepsy patients have been confronted with a proposal to switch their anti-epileptic medications at a pharmacy. More of them report negative attitudes towards the pharmacist's proposal than do not. It is possible that one of the major reasons for this is the insufficient information provided by pharmacists. It remains to be established whether the reported decrease in seizure control could be accounted for by a low concentration of the anti-epileptic drug in the blood after the switch.

Key words: antiepileptic drugs, patients, attitudes, pharmacy switch.

INTRODUCTION

Epilepsy is a disorder of the brain characterized by an enduring predisposition to epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition [1]. This widespread, chronic disease affects around 50 million people worldwide, nearly 80% of them living in low- and middle-income countries. It is estimated that up to 70% of people suffering from epilepsy could live seizure-free if accurately diagnosed and treated [2]. Achieving that goal requires systematic cooperation between a patient and neurologist and long-term, in many cases even lifelong, pharmacological treatment.

Switching original brand drugs for generics is a common practice in most healthcare systems [3]. According to the Food and Drug Administration (FDA) definition, a generic drug must be a chemically identical "copy" of a brand name drug and needs to demonstrate "pharmaceutical equivalence" (the same active ingredient, dosage, route of administration, strength) and bioequivalence (BE) [4], which means having pharmacokinetic properties comparable to the original formulation after administration.

The main reason for prescribing generic antiepileptic drugs (AEDs) is their lower cost. That is why the usage of generic medications is economically justified, and why in many countries it is legally allowed to switch antiepileptic medications at a pharmacy [5]. However, the difference in prices between original drugs and generics is smaller in countries with national health care systems such as Poland, where the market share of generics is one of the highest in Europe [6]. In this case the current availability of a drug is more important; when a pharmacy changes its supply source or a generic manufacturer exits, it is allowed to switch a prescribed AED for a different one that is available at the time [7]. This possibility has raised concerns about the safety and efficacy of treatment.

There are several reports indicating clinical risks associated with a substitution from the original anti-epileptic to a generic (and vice versa) or from one generic to another, such as: adverse events, breakthrough seizures, emergency department visits and hospitalizations [3, 8-12]. In addition to a potential deterioration of treatment effectiveness, a pharmacy switch may challenge a patient's compliance and lead to modifications in his/her anti-epileptic treatment scheme [6, 13]. However, many opinions on this issue are ambiguous or even contradictory. Kesselheim *et al.* [7] showed that generic AEDs appear to be safe clinical choices, and that changing the generic formulation, shape or color of tablets did not increase the occurrence of seizures. There are studies proving no association between generic medication change and higher risk of seizure-related hospitalizations [14], increased incidence of events or utilization changes [15], or significantly increased seizure frequency [16].

Krauss and Privitera's [17] analysis suggests that generic AED switching is generally safe. The purpose of this study was to assess the behavioral and clinical responses of patients with epilepsy towards an offer of changing a brand name AED to a generic one.

Table 1. Antiepileptic drugs taken by 211 patients recruited to the study

Drug	Patients (%)*
Lamotrigine	45.5
Valproate	41.7
Levetiracetam	40.3
Carbamazepine	26.5
Topiramate	13.3
Lacozamide	11.4
Oxcarbazepine	5.2

**Some patients were treated with more than one antiepileptic drug (1 AED – 49.3%, 2 AEDs – 41.7%, 3 AEDs – 12.8%; 4 AEDs – 4.3%). Only drugs used by more than 5% of patients have been listed.*

Table 2. Baseline characteristics of the final study group, i.e. 89/211 patients who were confronted with the proposal of drugswitch at a pharmacy

Variable	
Women (%)	57.3
Age (years)	38.44 ± 14.38*
University degree (%)	23.6
Currently employed (%)	47.7
Living with family (%)	91.0
Married or in stable relationship (%)	48.9
Age of onset of the first attack (years)	20.1 ± 18.9*
No. of hospitalizations	5.3 ± 7.7*
Taking more than one antiepileptic drug (%)	71.6

**Mean ± SD.*

METHODS

The survey study protocol was reviewed and accepted by the Ethics Committee of The Institute of Psychiatry and Neurology in Warsaw. All participants gave their written informed consent to participate in the research.

A structured questionnaire on the experience of and attitudes towards the pharmacy switching of anti-epileptic medications (for details, see Murawiec *et al.*, 2015) [18] was administered to a group of epilepsy patients treated at the Department of Neurology and Outpatient Clinics of the Institute of Psychiatry and Neurology and the Medical University of Silesia, Poland. Clinical and socio-demographic data were based on the interview and analysis of medical records.

Two hundred and eleven patients (mean [± SD] age: 41.0 ± 15.6 years) were recruited: 60.6% were women; 83.0% declared that they lived in cities; over 64.0% declared having at least a university education; and 58.0% were not professionally active. The average age of epilepsy onset was 23.4 ± 20.6 years; 68.2% of the patients had been treated for over 10 years. Most patients used at least 2 anti-epileptic drugs (range: 1 to 5) (Table 1). The data specific to the group of patients who received an offer to switch their antiepileptic drug at a pharmacy are shown in Table 2.

The questionnaire was divided into two parts. The first contained inclusion/exclusion criteria, the informed consent form and socio-demographic parameters. The second consisted of an interview with a clinician, regarding details of the drug substitution process. Only patients who responded positively to the 4th question – concerning the proposition that they buy a generic drug from a pharmacist – went on to the next part of the questionnaire (questions 5-11). Question 5 concerned the receipt or otherwise of any further explanations from a pharmacist about recommended generic drugs. Questions 6 to 8 described a patient's emotional and behavioral attitude and response to the drug switch (Table 3).

RESULTS

Eighty nine (42%) of the 211 patients recruited answered positively when asked if they had been offered by a pharmacist, in the previous year, an anti-epileptic medication named differently from that prescribed by their neurologist. These patients answered the other seven questions related to the pharmacy switch (items 5-11; Table 3) and the answers were analyzed further. Basic clinical and socio-demographic characteristics of the final study group (n = 89) are shown in Table 2.

Sixty (67.4%) of the 89 patients confronted with the proposal received some explanations from the pharmacist who proposed the switch of their medication.

Forty six patients (46/89, 51.6%) did not decide to change their medication. Forty three patients (48.3%) accepted the switch.

Table 3. Study questionnaire items related to a pharmacy switch (adapted from (18))

Questions below refer to your visits in pharmacy over the last 12 months with any prescription for antiepileptic medications received from your doctor:	
4) Were you offered by a pharmacist an anti-epileptic medication named differently from that prescribed by your doctor? If "Yes", please refer to the most recent or most remembered visit and answer the following questions. If "No", please do not answer the other questions.	Quantitative analysis of yes/no responses
5) Did you receive any explanations from a pharmacist proposing the switch of the anti-epileptic drugs prescribed by your doctor?	Quantitative analysis of yes/no responses
6) Did you accept this proposal?	Quantitative analysis of yes/no responses
7) What was your attitude to this proposal?	Quantitative analysis of responses on the Likert-like scale Very negative Negative Neutral Positive Very positive
8) What was your emotional response to the proposal?	Qualitative analysis of patients' descriptions
9) Did you inform your neurologist about this situation?	Quantitative analysis of responses No Yes, during an unscheduled visit Yes, during a scheduled visit
10) Did you notice any subjective changes in the drug's efficacy and/or tolerance after the switch?	Quantitative analysis of yes/no responses If "yes", qualitative analysis of patient's reports
11) Did you change the dose or dosing frequency of the anti-epileptic drug after the switch?	Quantitative analysis of yes/no responses

Attitudes towards the proposed switch were reported by all of 89 patients who qualified for the final study group. Thirteen subjects declared "very negative", 23 subjects declared "negative", 33 subjects declared "neutral", 14 subjects declared "positive", and 6 subjects declared a "very positive" attitude to the proposal.

Eighty-four of the 89 patients self-reported their emotional response accompanying the proposal. The self-reports were dominated by descriptions of negative emotions (34/84, 40.5%). The most frequent negative emotions, reported by 20 subjects, were "anger" and/or "fear". Fifteen of 84 self-reports referred to positive emotions associated with the pharmacy substitution. Positive emotions were mostly associated with the lower price of the new medication (5 patients).

Among patients who decided to change their antiepileptic medication (43/89, 48.3%), around 25.5% (11/43) did not inform their neurologist about the pharmacy switch. Twenty-nine subjects reported it during a scheduled visit (67.4%), and 3 of 43 (6.7%) during an additional unscheduled visit.

Most respondents who accepted the pharmacy switch (29/43, 67.4%) did not notice any change in the efficacy and tolerability of the treatment. Ten subjects who accepted the switch (23.2%) reported an increase in seizure frequency and four patients (9%) noted a deterioration in treatment tolerance.

Four of the 43 patients who accepted the switch (10.0%) decided to change the dose or dosing frequency of antiepileptic medication (3 to increase the dose, 1 to decrease the dose of the drug).

DISCUSSION

Generic drugs are commonly used worldwide by patients with almost every medical condition and are available in all drug categories, but using them as an epilepsy treatment seems to be a subject of special concern. It seems that people with epilepsy represent a unique group of patients because of their specific clinical profile and the natural course of the disease. The occurrence of seizures, especially when old drugs are used, is closely related to the stability of the drug concentration in plasma. Even 10% fluctuations in this can cause breakthrough seizures, with all their consequences such as head injuries or, in the most critical cases, even death [19]. Obviously, a 10% decrease in blood pressure medications, painkillers or statins will not have such an influence on clinical symptoms among patients with hypertension or hypercholesterolemia.

As already mentioned, the FDA demands that a generic drug formulation must fulfill the criteria of bioequivalence and demonstrate a similar plasma profile. The BE of 2 products is established when there is 90% confidence that the ratios of the maximum plasma drug concentration (C_{max}) and area under the drug plasma concentration curve (AUC) of original and generic drugs lie within the 80-125% range [6, 19, 20]. But these assumptions allow for a specified degree of variability, which can potentially cause therapeutic issues.

Bearing in mind that the first studies on BE and the safety of generic AED switches were performed in young, healthy people with a single dose of the investi-

gated substance, doubts arose as to whether this pharmacokinetic standard is sufficient for patients with epilepsy and for every antiepileptic medication.

Previous studies showed that this range may be too wide for drugs with an NTI (Narrow Therapeutic Index), with which even slight changes of blood concentration can have a big impact on clinical state and cause both toxic dose symptoms and seizures. Many agencies imposed thereafter stricter criteria of bioequivalence for NTIs. The European Medicines Agency guidelines tightened the acceptance interval for both AUC and C_{max} to 90-110%. There is no official list of NTIs, but carbamazepine, divalproex sodium, phenytoin, and valproic acid are certainly substances for which stricter bioequivalence requirements are necessary [21].

Except for the narrow therapeutic index presented by the above-mentioned drugs, some of the other pharmacokinetic properties of AEDs may be problematic in maintaining therapeutic drug concentration. These are: low water solubility, and nonlinear pharmacokinetic, excitatory, or inhibitory effects on hepatic enzymes [21].

Generic-to-generic switches may also be associated with shifts of drug concentrations because their bioavailability between formulations can differ to a greater extent than those between brand name drugs and generics [19, 22].

Generally speaking, the generics of new generation AEDs seem, thanks to their pharmacokinetic profiles, to be more easily bioequivalent to the original drug and to each other, and they are relatively less problematic during the switching process [19].

Reimers *et al.* [23] examined, in a prospective 18-week study, 33 patients treated with Keppra – original levetiracetam (LEV). After 10 weeks, 16 of them were switched to generic levetiracetam for an eight-week period. Both groups were monitored for LEV serum concentration and kept seizure diaries. Fluctuations in LEV serum concentrations were not larger with generic LEV products than with branded LEV. What seemed to be more important was that variability within-subject was much larger than small differences within brands. None of the seizure-free patients experienced seizures during the substitution. Also, no switchbacks were observed [23]. A prospective study [24] investigated possible changes in quality of life (QoL) and adverse reactions following a generic substitution of levetiracetam. They found that no significant deterioration in QoL or increase of frequency in adverse events appeared, nor were any switchbacks observed.

Hartung *et al.* [25] investigated a cohort of 616 sustained lamotrigine (LTG) users (for 2 years and more). Forty one percent of the subjects suffered from epilepsy. A conversion from the original brand to a generic was not associated with a statistically significant increase in ED visits, hospitalizations, and condition-specific encounters.

In a trial assessing the safety of switching from brand-name to generic levetiracetam (LEV) in patients with epilepsy, Bosak *et al.* [26] analyzed a group of 151 patients. An increased frequency of seizures occurred in 9 patients (6%). Different adverse events were observed in 6 other cases.

Another study evaluating the risk of increased frequency of seizures after switching original levetiracetam for a generic was conducted in 2018 [16]. Among 148 patients with epilepsy, 109 (73.8%) were seizure-free before drug replacement and 105 remained seizure-free after switching. Furthermore, the authors observed a reduction in seizure frequency in 10 patients, while 7 subjects had shown an increased occurrence of seizures. The main conclusion was that the substitution of LEV was generally safe, although larger prospective studies are needed.

Rahman *et al.* [4] included in their analysis reports of adverse reactions to lamotrigine, carbamazepine (CBZ) and oxcarbazepine (OXC) in the U.S. Food and Drug Administration Adverse Events Reporting System (FAERS). The authors compared 46,177 reports from the period 2004 to 2015. Data included 27,150 reports for LTG, 13,950 for CBZ and 5,077 for OXC. No significant differences in efficacy and seizure control between generics and brand name products were found. Adverse effects were comparable, with the exception of the stronger suicidal tendencies observed among generics users. This observation needs more evidence, because no other study has yet evaluated the risk of suicidality across brand vs. generic AEDs.

Because the study results regarding this kind of medication switching have not been unequivocal, both patients and doctors nowadays face the challenge of changing original brands with generic products which may potentially increase the risk of severe therapeutic failures such as breakthrough seizures, unscheduled ambulatory or emergency department visits and hospitalizations [27]. A systematic review of retrospective studies in medical databases presented inconsistent findings: three articles proved an association between a switch of original topiramate and an increase in healthcare utilization, and another 3 studies found no connection between switching brand name lamotrigine to generic and an increase in emergency events. Pooled studies resulted in conflicting outcomes – 5 of them reported increased healthcare utilization and 5 did not [28].

We should also consider the fact that an appearance of seizures or adverse events while switching a brand name AED for a generic may not be connected with its pharmacokinetics alone. It could also be a reflection of the natural course of the disease. Another reason might be patients' non-adherence as a result of confusion caused by changes in the shape or color of medications [6, 17]. Last but not least, there is the phenomenon of 'nocebo effect' – if patients are warned by a physician or pharmacist about a possible loss of effectiveness or occurrence of side effects after switching a brand name AED for a generic, they may be extremely watchful,

and prone to focus more on potential adverse events, becoming meticulous in counting and reporting seizures and falsely connecting coincidental symptoms to the medication switching [22, 24].

In our study 50% of patients did not decide to change their medication after receiving such a proposition from a pharmacist. A recent Swedish survey study [29] looking for associations between the characteristics of people with epilepsy and their attitudes toward switching AEDs for generics showed that almost 46% of 178 subjects were against drug substitution, and that 71% were afraid of an increased risk of a higher frequency of seizures or adverse effects after pharmacotherapy modification. Furthermore, opposition to drug substitution and worries about the efficacy of therapy and adverse events had a negative association with education (high school or higher level), occupation, and previous experience of AED switching.

Physicians' knowledge and attitude towards generic switching probably influences the use of generics. One systematic review of the available data has shown that doctors believed generics caused more side effects than branded medication and had significantly more safety concerns about generics than did lay people. It is interesting that rates of negative perceptions of generics do not appear to have changed substantially over time [30]. Another review has pointed out that the maturity of country's healthcare system may influence the awareness of physicians and pharmacists of the role of generic medications in the improvement of global access to drugs [31].

The question of the safety of substitution of brand name AEDs is a live issue which has been discussed for the last 40 years by Epileptic Associations in the U.S. and Europe. Based on a literature review [27], many epilepsy societies and agencies worldwide recommend that patients with well-controlled epilepsy should avoid switching from brand-to-generic, generic-to-brand and generic-to-generic, and some of them pay special attention to the monitoring of drug levels in the blood. It appears that these rules should be strictly obeyed among "high risk patients" such as pregnant women, those with multiple disorders taking many other medications, and people of extreme age [27].

CONCLUSIONS

Around 40% of Polish epilepsy patients had been confronted with a proposal to switch their anti-epileptic medications at a pharmacy in the previous 12 months, and more than 40% of them reported negative attitudes and expressed negative emotions (including fear of deteriorating seizure control) towards a pharmacist's proposal that they switch drugs.

It is possible that one of the major reasons for the patients' negative attitudes was the insufficient information provided by pharmacists. It remains to be established whether the decrease in seizure control reported by 23.2% of subjects who accepted the pharmacist's proposal could be justified by a low concentration of anti-epileptic drugs after the switch, or perhaps the coexistence of other factors such as the natural course of the disease or patients' non-adherence.

Conflict of interest

Absent.

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