



## An assessment of patient and pharmacist knowledge of and attitudes toward reporting adverse drug events due to formulation switching in patients with epilepsy

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### ABSTRACT

A survey was developed to gather information from both patients with epilepsy and community pharmacists on the issue of antiepileptic drug (AED) formulation switching, which includes brand to generic, generic to brand, and generic to generic. Data were obtained from 82 patients (or parents of patients) with epilepsy and 112 community pharmacists. More than 92% of patients and 85% of pharmacists agreed that switching between forms of the same AEDs may cause an increase in seizures or adverse effects. More than two-thirds of our patient sample reported having problems with formulation switching; many also reported knowing other patients with problems. Just more than half (51%) of the pharmacists knew of patients who have described problems when they have changed AED formulations. Less than 50% of both populations knew that problems resulting from formulation switching should be reported as adverse drug events to the FDA. Not many pharmacists and far fewer patients use MedWatch to report these problems. We conclude that both patients with epilepsy and pharmacists are underinformed and underinvolved with reporting adverse drug events.

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### 1. Introduction

Epilepsy is a common neurological problem affecting 1–2% of the U.S. population. Epilepsy has significant social and economic consequences. These can be minimized by optimal seizure control. Antiepileptic drugs (AEDs) are the mainstay of treatment in this chronic disease. Treatment goals for patients with epilepsy include the prevention of seizures, the reduction and/or prevention of adverse drug events and drug interactions, improvement of quality of life, and patient satisfaction [1]. AED therapy should also be cost-effective. One popular strategy to contain costs involves AED generic substitution [2]. Although the need to cut cost is recognized, it is important that patient care not be compromised in the process [3]. Going beyond generic substitution is the larger issue of formulation switching, which includes changing from brand to generic, generic to brand, and generic to generic.

Because of the Food and Drug Administration's designation of drugs as bioequivalent, it is generally believed that different formulations of the same product are entirely equivalent and inter-

changeable. Although this may be an accurate statement for many drug products on the market, it may not be entirely accurate with AEDs. Finding the right balance between preventing seizures and minimizing adverse effects in most patients with epilepsy is a complex and sometimes lengthy process. This balance can be affected when an AED formulation is changed.

The variance in bioequivalence allowed by the FDA may result in the fluctuation of AED concentrations. This fluctuation, although not clear how prevalent or clinically significant, can result in lower AED concentrations with resultant seizures or higher AED concentrations and subsequent toxicity [2]. Many patients with epilepsy do not tolerate such fluctuations. Many physicians and patients have expressed concern regarding AED formulation switching [4–6]. However, the scope of any negative impact of such switching is not systematically documented in the medical literature. Adverse drug events (either seizures or toxicity) resulting from AED formulation switching should be reported to the FDA. It is our opinion that problems with switching go underreported by both patients and health care professionals.

Education for the patient and the many health care professionals involved in the care of the patient with epilepsy is an important aspect of reporting adverse events. As medications play a major role in the treatment of epilepsy, pharmacists serve an important function in the care of patients with this chronic disease.

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Pharmacists should take advantage of the opportunity to expand their roles in providing optimal care to their patients with epilepsy [7]. Reporting adverse drug events with AED formulation switching through the FDA's Safety Information and Adverse Event Reporting Program (MedWatch, [www.fda.gov/medwatch](http://www.fda.gov/medwatch)) is an example of how this expanded role can be achieved. Many physicians are unaware that the FDA has established MedWatch, and others have called for enhanced reporting by physicians as a way to inform the FDA and push for action [8]. In a recent article, Carreno and colleagues demonstrate that asking patients with epilepsy about adverse events is a better strategy for detecting these events as compared with spontaneous reporting by patients [9].

We developed a survey instrument to gather information from both patients and pharmacists. Our goal of this educational project was to assess both populations' knowledge of and attitudes toward AED formulation switching and reporting of adverse drug events to the FDA.

## 2. Methods

We conducted a cross-sectional study asking both pharmacists and patients to respond to a brief survey. Approval from the Ohio State University's Biomedical Institutional Review Board was obtained and a waiver of consent granted.

### 2.1. Patient survey

Patients or parents of patients with epilepsy were recruited from the Epilepsy Foundation of Central Ohio's database. A 21-question survey was developed in Zoomerang ([www.zoomerang.com](http://www.zoomerang.com)). The survey began with the definition of formulation switching as "1. Switching from a brand name to a generic drug, 2. Switching from a generic to a brand name drug, or 3. Switching from one generic to another generic drug." The survey was confidential and voluntary. The first 13 questions asked about their knowledge of and attitudes toward switching between forms of the same AEDs and reporting adverse drug events resulting from switching. The last 8 questions elicited demographic information and the number of generic and brand name AEDs currently being used. E-mails with a link to the Zoomerang survey were sent to 250 patients and the survey site was open for 6 weeks.

### 2.2. Pharmacist survey

We obtained an electronic copy of the Ohio State Board of Pharmacy's database of registered pharmacists, containing more than 15,000 pharmacists' names, addresses, and practice settings. As we felt this issue impacted community pharmacy practice the most, we focused on the pharmacists who reported their practice type to be one of the following: "independent community pharmacy," "small chain," "large chain," and "clinic or medical center." From those 5890 pharmacists, we randomly selected 125 from each of the four community pharmacy practice types. The pharmacists were mailed a cover letter, a brief 19-question survey, and a postage-paid return envelope. The survey was confidential and voluntary. As in the patient survey, the cover letter defined formulation switching. The first 12 questions dealt with their knowledge of and attitudes toward AED formulation switching and reporting adverse events. The last 7 questions elicited demographic information. Surveys were collected over 6 weeks.

### 2.3. Data analysis

Descriptive statistics were used to characterize the demographic data and responses by population.

## 3. Results

### 3.1. Patient survey

Data were obtained from 82 patients (or parents of children) with epilepsy using the online data collection method; this reflects a response rate of 33%. Table 1 summarizes demographic details on the patient respondents. The average age of the respondents was 27.1 years, and most were women (57%). The largest portion of the patients who responded were on AED monotherapy (41%), with a majority not currently taking any generic AED products (70%).

Table 2 lists the questions and patient responses. Most patients (62%) did not agree with the statement that formulation switching, in general, is safe. Nearly all (99%) agreed that finding the right dose of the right drug to prevent seizures can sometimes be difficult and can take awhile. More than 95% of patients agreed that switching between forms of the same AEDs may cause an increase in seizures or adverse effects. When patients were asked about their personal experience with problems resulting from formulation switching, more than 40% reported such problems; a similar number knew of other patients who experienced problems as well. Of note, more than one-third of the patient respondents reported that these statements did not apply to them.

Slightly less than half of the patients (47%) knew that problems resulting from formulation switching should be reported as adverse drug events. Very few patients (6%) knew about the FDA's MedWatch program designed to allow patients and practitioners to report adverse drug events before they took the survey. Only one patient of the 82 reported using the program, and this was for reporting problems with formulation switching. More than half of the patient respondents saw a role for themselves in reporting problems through MedWatch (59%), and the majority were not dissuaded by the amount of time needed to complete the form (67%). Willingness to use MedWatch was reported by most patients (75%), and more than 70% were interested in learning more about the FDA program.

We asked patients who responded "yes" to the question about whether they saw a role for themselves in reporting adverse drug events using MedWatch to provide comments; 27 of the 82 chose to do so. Most patient comments centered on their desire to advocate for themselves and others along with a general desire to help

**Table 1**  
Demographics of patient respondents ( $n = 82$ )

Age	27.1 (17.2) <sup>a</sup>
Years taking antiepileptic drugs	12.9 (12.9) <sup>a</sup>
Sex	
Men	38%
Women	57%
Not reported	5%
AEDs currently being taken	
One	41%
Two	38%
Three or more	21%
Generic AEDs currently being taken	
Zero	70%
One	18%
Two	4%
Three or more	3%
Not sure	5%
Brand name AEDs currently being taken	
Zero	10%
One	44%
Two	27%
Three or more	10%
Not sure	9%

<sup>a</sup> Mean (SD).

**Table 2**  
Patients' (n = 82) survey responses

Survey question	%
In general, formulation switching with most medications is safe	
Agree	38
Disagree	62
Finding the right dose of the optimal treatment to prevent seizures in a patient with epilepsy can be a complex and sometimes lengthy process	
Agree	99
Disagree	1
Switching between forms of the same antiepileptic drugs may cause an increase in seizures OR side effects.	
Agree	96
Disagree	4
I have experienced problems when switching between the same forms of my antiepileptic drug(s)	
Yes	43
No	19
Not applicable	38
I know other patients who have experienced problems when switching between the same forms of their antiepileptic drugs	
Yes	48
No	17
Not applicable	35
Did you know that problems with switching between the same forms of antiepileptic drugs should be reported as adverse drug events?	
Yes	47
No	53
The FDA has a safety information and adverse event reporting program called MedWatch. It allows patients to report adverse drug events. Did you know about this program before today?	
Yes	6
No	94
Have you used the MedWatch program?	
Yes	1
No	99
Do you see a role for yourself in reporting adverse drug events through MedWatch?	
Yes	59
No	41
It is estimated to take 20–40 minutes to fill out a MedWatch form. Does this fact deter you from using the program?	
Yes	33
No	67
After learning more about the MedWatch system, are you more or less willing to use it?	
More	75
Less	25
I am interested in learning more about switching between the same forms of antiepileptic drugs	
Yes	50
No	50
I am interested in learning more about the MedWatch system	
Yes	74
No	26

others (n = 25). Other patients described a desire to heighten awareness of the potential problems and were interested in “getting the word out” (n = 2).

### 3.2. Pharmacist survey

Some of the returned pharmacist surveys were not used because the pharmacists were no longer living in Ohio, were no longer practicing pharmacy, or were not practicing pharmacy in one of our targeted community pharmacy areas, or the returns came in past the 6-week deadline. Data from 112 of the 500 mailings were used in our analysis, representing a response rate of 22%. Our sample consisted of more men (58%) than women (42%), who, on average, saw slightly more than 20 patients with epilepsy per month and were in their current community pharmacy practice setting for more than 17 years. The largest portion of the responding sam-

**Table 3**  
Demographics of pharmacist respondents (n = 112)

Age (years)	47.3 (13.8) <sup>a</sup>
Years in current practice setting	17.2 (12.3) <sup>a</sup>
Patients with epilepsy seen per month	20.6 (26.3) <sup>a</sup>
Sex	
Men	58%
Women	42%
Practice setting	
Independent community pharmacy	38%
Small chain	17%
Large chain	27%
Clinic/medical building	18%

<sup>a</sup> Mean (SD).

ple worked in independent community pharmacy practice (38%). Table 3 provides more demographics on the community pharmacists.

Table 4 lists the questions and pharmacist responses. In contrast to the patients, nearly all pharmacists agreed that, in general, it is safe to switch formulations with most medications (96%). Ninety-eight percent of the pharmacists agreed that finding the right dose of the right drug to prevent seizures in patients with epilepsy can be difficult and can sometimes take awhile (98%). More than 85% of pharmacists agreed that switching between forms of

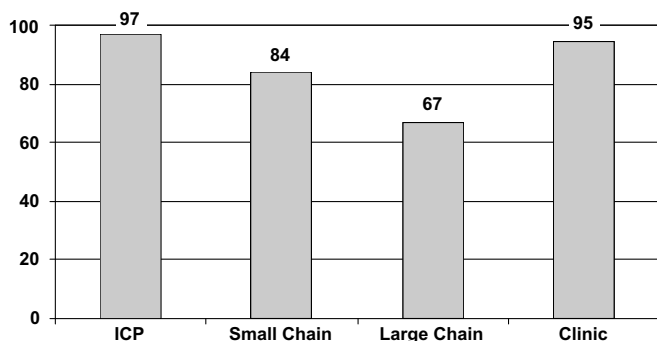
**Table 4**  
Pharmacists' (n = 112) survey responses

Survey question	%
In general, formulation switching with most medications is safe	
Agree	96
Disagree	4
Finding the right dose of the optimal treatment to prevent seizures in a patient with epilepsy can be a complex and sometimes lengthy process	
Agree	98
Disagree	2
Switching between forms of the same antiepileptic drugs may cause an increase in seizures OR side effects	
Agree	87
Disagree	13
Patients with whom I have interacted have described problems when they have changed antiepileptic drug formulations	
Yes	51
No	49
Did you know that problems with switching between the same forms of antiepileptic drugs should be reported as adverse drug events?	
Yes	41
No	59
The FDA has a safety information and adverse event reporting program called MedWatch. It allows patients to report adverse drug events. Did you know about this program before today?	
Yes	79
No	21
Have you used the MedWatch program?	
Yes	27
No	73
Do you see a role for yourself in reporting adverse drug events through MedWatch?	
Yes	88
No	12
It is estimated to take 20–40 minutes to fill out a MedWatch form. Does this fact deter you from using the program?	
Yes	55
No	45
After learning more about the MedWatch system, are you more or less willing to use it?	
More	85
Less	15
I am interested in learning more about switching between the same forms of antiepileptic drugs	
Yes	67
No	33
I am interested in learning more about the MedWatch system	
Yes	68
No	32

**Table 5**

Type and frequency of comments provided by pharmacists when asked why they do or do not see a role for themselves in reporting adverse events through MedWatch

Reason	Frequency
Pharmacists who see a role for themselves	
Patient safety/increase awareness of problems	36
Pharmacist's professional responsibility/"right thing to do"	16
Pharmacist's ready access to patients	6
Pharmacists who do not see a role for themselves	
Too busy	2
Someone else's responsibility: not mine, should be patient or physician	2
Not familiar with MedWatch	2
Not enough patient information	2
Too lengthy	1
Too confusing	1



**Fig. 1.** Percentages of pharmacists, by practice setting, who responded "yes" to the question "Do you see a role for yourself in reporting adverse drug events through MedWatch?" ICP, independent community pharmacy.

the same AEDs may cause an increase in seizures or adverse effects. Interestingly, more than half (51%) of the pharmacists in our sample knew of patients who described problems when they changed AED formulations.

Only 41% of the pharmacists knew that situations involving patients experiencing problems with AED formulation switching should be reported as adverse drug events. Almost 80% of the pharmacists knew about the MedWatch program before the survey; whereas only 27% reported previously using the MedWatch program. Only one pharmacist reported previously using MedWatch to report a patient who was experiencing problems with formulation switching. Nearly 9 of 10 respondents (88%) stated that they saw a role for themselves in reporting problems through MedWatch, though 55% were deterred by the amount of time needed to complete the information. There was an overwhelming willingness to use the MedWatch system more frequently.

Table 5 summarizes the comments from pharmacists asked if they did or did not see a role for themselves and why in reporting adverse drug events using MedWatch. As can be seen, most of the respondents who provided written comments to the "Why?" question were positive in their responses, though some were negative. As can be seen from Fig. 1, there were fewer pharmacists practicing in large chain settings (67%) who saw a role for themselves in reporting problems using MedWatch compared with the three other community pharmacy practice settings.

#### 4. Discussion

Our study indicates that 62% of patients do not feel safe with switching between AED formulations. This feeling reflects either a bad experience with AED formulation switching, knowing someone who had a bad experience, or a negative attitude toward

switching. Though only asking about part of the formulation switching issue, Haskins and colleagues surveyed patients with epilepsy, and when asked about generic AEDs, 66 and 68% of the patients were concerned about safety and effectiveness [6].

An interesting finding from our study is the high percentage of patients who experienced problems with formulation switching. Of the patients who responded "yes" or "no" to the question about experiencing problems when switching between AED formulations (62% of patient respondents), nearly 70% (43%) reported experiencing problems. Obviously it is very hard to verify these numbers and how clinically significant the problems were. Similarly, slightly more than half of the surveyed pharmacists (51%) reported interacting with patients who experienced problems on formulation changes. This was higher than we expected. In a survey of neurologists, 68% reported breakthrough seizures and 56% reported increased adverse effects in patients after a switch from brand to generic [5]. If the results from these reports (significant problems on formulation switching) can be confirmed in systematic prospective studies, one could argue strongly against AED formulation switching in all patients with epilepsy.

We find it noteworthy that nearly all (96%) of the pharmacists agreed that, in general, formulation switching is safe, yet most (87%) also agreed that switching between forms of the same AEDs may cause an increase in seizures or side effects. These data, combined with the relatively high frequency of known problems reported by pharmacists (51%), could be interpreted as indicating that many pharmacists consider AEDs in a separate or "non-interchangeable" drug category. This notion of exemption from substitution is not new. Some form of it exists in many countries worldwide [3].

Almost all patients were not aware of MedWatch, which is not surprising. We are not aware of any clinical practice, including ours, that informs patients about reporting adverse effects through this FDA program. An encouraging finding was the patients' desire to learn more about MedWatch and their desire to play an active role in reporting adverse events. This was the case even though the patients were told the MedWatch reporting system may take 20 to 40 minutes to complete.

An unexpected finding was that 21% of pharmacists were not aware of the MedWatch reporting program and that only 27% have used it in the past. Taking the time to use MedWatch was identified as a deterrent by 55% of the pharmacists. The percentage may be higher given that 73% have not used it at all. Lack of time was identified as a significant barrier by pharmacists to providing care to patients with epilepsy in the past [7]. The time issue is completely understandable, and probably similar results would be obtained if physicians were surveyed [8]. Interestingly, as can be seen from Fig. 1, the place where community pharmacists practice may influence their willingness to use the program. The group with the highest positive response was independent community pharmacists, and those with the least positive response were pharmacists working in large chain practice settings. Though we did not ask them to report on the busyness of their practice, one might assume that the pharmacists in the large chain settings have less time than those in the independent setting.

It may be inevitable that many patients will have to deal with AED formulation switching, especially as many of the newer AEDs are off patent now or will be going off soon. One could take the position that there may be positive economic features and probably even some positive clinical aspects (improved adherence in patients who previously could not afford their AEDs because they were underinsured or not insured). However, formulation switching may have a negative impact, both economically and clinically [5]. The positive economic impact is obvious, but the negative aspect needs to be more clearly documented and certainly weighed against the positive. It is the epilepsy community's responsibility

(both patients and health care professionals) to document any negative impact of AED formulation switching. Prospective studies, though not easy to do, would be optimal to document such an impact. Reporting any adverse events from formulation changes to the FDA through MedWatch is a good place to start. In our survey, the majority of both patients and pharmacists expressed an interest in reporting adverse events.

It would be beneficial to engage patients with epilepsy (and their families and/or caregivers) about the importance of being involved in advocating for themselves and others. Many of our patient respondents were altruistic in their provided comments. Persons who are motivated to report their adverse experiences could be provided with resources explaining how to access MedWatch. The MedWatch program has both a web-based reporting system and a paper-based system. Health care professionals (including pharmacists) involved in their care could easily provide information and/or guidance when they encounter patients who have experienced problems resulting from AED formulation switching. It is also important to encourage patients to report adverse events not only to their physicians but also to their community pharmacists. Taking the active approach of asking patients with epilepsy about adverse events is better than the passive approach of spontaneous reporting by patients [9].

It is plausible to think about also using technology to allow pharmacists to more efficiently report adverse drug events so they may be more willing to do it. For example, many health care systems have combined MedWatch with their own adverse event reporting system to allow for a more efficient process.

Pharmacists acknowledge their interest in helping patients as well as their professional role in reporting such events. Educational programs like continuing education opportunities could be provided to pharmacists. One idea to further pursue is that the American Epilepsy Society and/or the Epilepsy Foundation of America could conduct a campaign to encourage clinical practices and pharmacies to provide patients with information on reporting adverse effects through MedWatch. This campaign could be conducted in collaboration with the FDA. Overcoming barriers to reporting adverse drug events is likely the most important challenge. Pharmacists in busy practices are likely to have time limitations for reporting events. They may be able to encourage a greater role for patient involvement in reporting.

Our study is not without limitations. It was a cross-sectional study and thus did not track patients' or pharmacists' responses over time; they were asked their opinions just once. We did not validate the survey questions we developed. Our response rates for patients (33%) and pharmacists (22%) were less than optimal. For the patient population, we were limited to Central Ohio patients and those with Internet access. For the pharmacists, we sampled only those from Ohio, and thus, our data may not be applicable to all pharmacists across the country.

Based on their knowledge of and attitudes toward AED formulation switching and reporting of adverse drug events, we conclude that both patients with epilepsy and pharmacists are underinformed and underinvolved.

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