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Breakthrough Seizures in Patients Switched from Brand to Generic Antiseizure Medications

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ABSTRACT

Background: Despite the fact that generic drugs are less expensive than brand-name drugs, the healthcare system still does not employ enough generic drugs to treat seizures. The objective of the current study is to evaluate the relation between seizure-related outcomes and switching between brand name antiseizure medications (ASMs), and a different generic ASMs manufacturer.

Patients and methods: In a prospective cohort study conducted in Outpatient clinic of Neurology Department, Zagazig University Hospitals, 380 known epileptic patients were included. Cases were divided into 5 equal groups (76 cases in each group): *Group I* carbamazepine, *Group II* levetiracetam, *Group III* topiramate, *Group IV* valproic acid, and *Group V* lamotrigine. All included patients were evaluated for the effect of switching from a brand to generic ASMs.

Results: Mean duration of treatment with ASMs among study population was 13.72 (SD 6.52) years and ranged from 1 to 38 years. Only 19.2% of our study population had switched from brand-name to generic formulations under patients' their free will, due to unavailability of brand drugs, increase adverse effect, or financial issues. Regarding studies ASMs (carbamazepine, levetiracetam, topiramate, valproic acid and lamotrigine), we found statistically significant increased total seizure frequency after 6 months treatment, and breakthrough state among group shifted to generics. **Conclusion:** There is a potential association between the risk of breakthrough seizures and switching from brand to generic ASMs.

Keywords: Breakthrough seizures, Antiseizure Medications, Carbamazepine, Levetiracetam, Topiramate, Valproic acid, Lamotrigine, Generic drugs.

INTRODUCTION

In order to qualify as having epilepsy, a person must have at least two unprovoked (or reflex) seizures that happen more than 24 hours apart. one unprovoked (or reflex) seizure and a likelihood of additional seizures equal to the general recurrence risk (at least 60%) following two unprovoked seizures occurring over the course of the following 10 years, or the identification of an epilepsy syndrome [(1)].

After stroke and dementia, epilepsy is the third most prevalent neurological condition, affecting over 70 million people globally, or 0.5-1% of the population [(2)].

According to the FDA, a generic medicine is one that has the same dosage form, safety, strength, administration method, quality, performance attributes, and intended use as a brand-name drug [(3)].

Generic medications often cost between 20% and 90% less than their brand-name counterparts. For patients who are without health insurance or who are economically disadvantaged, the cost of generic ASMs is crucial. Generic drugs and go into a distinct tier that is more patient-affordable, while brand drugs fall into a tier that raises expense to patients [(3)].

Although brand-name vs generic drugs are thought to be more cost-effective, the US healthcare system still does not encourage consumer usage of generic drugs. There are several factors at play when customers decide whether to utilize generic drugs instead of name brands. The main concern is the notion that generic medications are less reliable or efficient than their brand-name counterparts. Other studies showed that most patients just don't like to utilize generics. Patients also think older drugs are safer than newer ones since they have been on the market longer. Additionally, patients who are in better condition are more worried about the effectiveness of generic drugs, much as older individuals who prefer brand-name drugs to generic ones [(4)].

The aim of this study is to evaluate the relation between seizure-related outcomes and switching between brand name antiseizure medications (ASMs), and a different generic ASMs manufacturer.

PATIENT AND METHOD

In a prospective cohort study conducted in Outpatient clinic of Neurology Department, Zagazig University Hospitals, 380 known epileptic patients were included. Cases were divided into 5 equal groups (76 cases in each group): *Group I* carbamazepine, *Group II* levetiracetam, *Group III* topiramate, *Group IV* valproic acid, and *Group V* lamotrigine. All included patients were evaluated for the effect of switching from a brand to generic ASMs.

Inclusion criteria:

- Adult patients 18years or older, both genders.
- Patients known case of epilepsy (of any type) on monotherapy ASMs.
- Patients on only one of the following ASMs; carbamazepine, levetiracetam, topiramate, valproic acid, and lamotrigine. All selected ASMs have generic products available in Egyptian pharmaceutical market, using immediate release form of the drug.

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Exclusion criteria:

- Patients less than 18years old.
- ASMs prescribed for chronic pain, migraine, or psychiatric diseases such as bipolar disorders.
- Patients on more than one ASMs.
- Patients on extended-release form.
- Patients with acute symptomatic seizures.
- Patients with renal, liver disease.

Each individual was examined thoroughly, including their history and their nervous system. A questionnaire sheet was prepared to investigate each patient, it is divided into two parts: The first part of the questionnaire is concerned with demographic characteristics such as (age, gender), and the second part is concerned with information about patient's disease, medications, seizures. Laboratory investigations (serum electrolytes, glucose, creatinine, CBC), computerized electroencephalogram (EEG), and radiological investigations (MRI brain) were done.

There was an evaluation of the effect of a switch from a brand to generic ASMs, defined as a dispensing of the same dose and the same formulation of the same ASM, but from a different manufacturer. Change in medications was done by the patient due to financial problems or unavailability of brand ASM. Follow up of patients was done for 6 months for monitoring of possible occurrence of breakthrough seizures in patients who were switched from brand to generic ASMs.

Ethical consent:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (IRB Approval No. #9197/23-1-2022). Written informed consent was taken from all participants. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 20 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher's exact test to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean and standard deviation (SD). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value $\leq$ 0.05 was considered significant.

RESULTS

Table 1 shows that 72.6% of studied group were males with mean age 38.54 (SD 10.02) years.

Table (1): Demographic characteristics of the studied group.

Variables		**Studied group (N= 380)**	
Age **Mean± SD** **Median (Range)**		**38.54±10.02** **40.0 (18-62)**	
		N	**%**
Sex	Male	**276**	**72.6**
	Female	**104**	**27.4**

Table 2 shows that the commonest causes of shift and frequency of cases shifted back to their original drug.

Table (2): Causes of shift and shift back among studied group.

Variables		**Number of cases shifted to generic name N=73**	
		N	**%**
Causes of shift to generic name	**High drug cost**	**50**	**68.5**
	Unavailability of drug	**19**	**26.0**
	Unspecific reason	**4**	**5.5**
Shift back	**Yes**	**32**	**43.8**
Causes of shift back	**Intolerability of drug**	**9**	**28.1**
	Increased seizure	**22**	**68.8**
	Unspecific reason	**1**	**3.1**

Only 6.8% admitted to hospitals due to status epilepticus and 21.6% had breakthrough seizures (**Figure 1**).

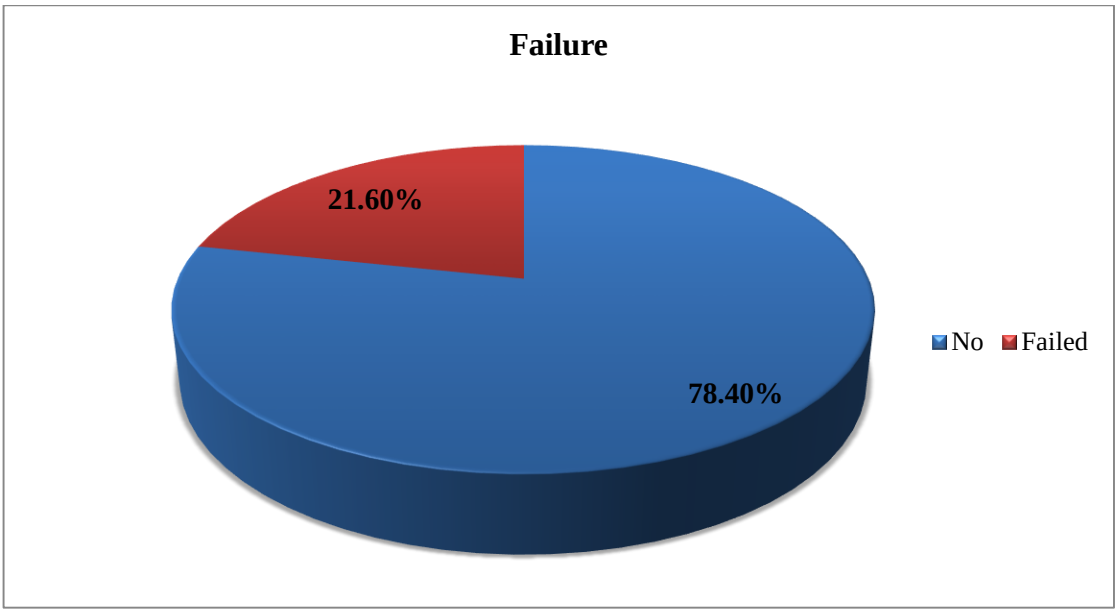

Figure (1): Status epilepticus (hospitalized patients) and breakthrough seizures (failed cases) distribution among studied group.

Table 3 shows statistically significant increased age, disease duration, baseline seizure and total seizure frequency after 6 months treatment among group shifted to generic name, also 20.5% of shifted group hospitalized during treatment period (due to status epilepticus) versus 3.6% of not shifted group with significant difference between them. Frequency of breakthrough was 47.9% of shifted group versus 15.3% of not shifted cases with high statistically significant difference.

Table (3): Association between patient characteristics and shift to generics among studied group.

Variable		Shifted group N=73	Not shifted group N=307	t-test/ MW*	P-value
Age		41.4 ± 8.77	38.4 ± 9.61	2.01	0.045 S
Duration		15 (2-31)	12 (1-38)	2.39*	0.02 S
Baseline seizure		1 (1-5)	1 (1-4)	4.92*	<0.001 HS
Total seizure after 6 months		0 (0-11)	0 (0-6)	6.33*	<0.001 HS
		N (%)	N (%)	X^2 test	
Sex	Male	57 (78.1%)	219 (71.3%)	1.37	0.27 (NS)
	Female	16 (21.9%)	88 (28.7%)		
Treatment group	Carbamazepine	17 (23.3%)	59 (19.2%)	2.14	0.711 (NS)
	Levetiracetam	11 (15.1%)	65 (21.2%)		
	Topiramate	16 (21.9%)	60 (19.5%)		
	Valproic acid	13 (17.8%)	63 (20.5%)		
	Lamotrigine	16 (21.9%)	60 (19.5%)		
Status epilepticus		15 (20.5%)	11 (3.6%)	26.6	<0.001 (HS)
Breakthrough status		35 (47.9%)	47 (15.3%)	37.1	<0.001 (HS)

NS: P-value>0.05 is not significant S: P-value<0.05 is significant HS: P-value<0.001 is high significant.

Table 4 shows statistically significant increased baseline seizure, total seizure frequency after 6 months treatment, status epilepticus rate and breakthrough status among group shifted back after shift to generic name.

Table (4): Difference between shifted and shifted back cases as regard patients' characteristics.

Variable		Shifted back group N=32	Not shifted back group N=41	t-test/ MW*	P-value
Age		**40.7 ± 9.17**	**41.9 ± 8.51**	**0.61**	**0.45 NS**
Duration		**14.5 (3-31)**	**15 (2-30)**	**0.59***	**0.52 NS**
Baseline seizure		**2 (1-5)**	**1 (1-5)**	**4.24***	**<0.001 HS**
Total seizure after 6 months		**3 (0-11)**	**0 (0-9)**	**4.93***	**<0.001 HS**
		N (%)	**N (%)**	**X^2 test**	
Sex	**Male**	**26 (81.2%)**	**31 (75.6%)**	**0.337**	**0.78 NS**
	Female	**6 (18.8%)**	**10 (24.4%)**		
Treatment group	**Carbamazepine**	**8 (25.0%)**	**9 (22.0%)**	**1.514**	**0.814 NS**
	Levetiracetam	**3 (9.3%)**	**8 (19.5%)**		
	Topiramate	**7 (21.9%)**	**9 (22.0%)**		
	Valproic acid	**6 (18.8%)**	**7 (17.1%)**		
	Lamotrigine	**8 (25%)**	**8 (19.5%)**		
Cause of drug shift	**High cost**	**14 (43.8%)**	**36 (87.8%)**	**17.7**	**<0.001 HS**
	Drug unavailability	**16 (50.0%)**	**3 (7.3%)**		
	Unspecific cause	**2 (6.2%)**	**2 (4.9%)**		
Status epilepticus		**11 (34.4%)**	**4 (9.8%)**	Fisher's	**0.02 S**
Breakthrough status		**27 (84.4%)**	**8 (19.5%)**	**30.1**	**<0.001 HS**

Number of seizures was significantly higher among valproic acid group in 3rd, 6th month, and seizures are significantly higher among valproic acid and Carbamazepine groups in total during study period, also valproic acid group associated with higher breakthrough seizures than other groups but statistically not significant (**Figure 2**).

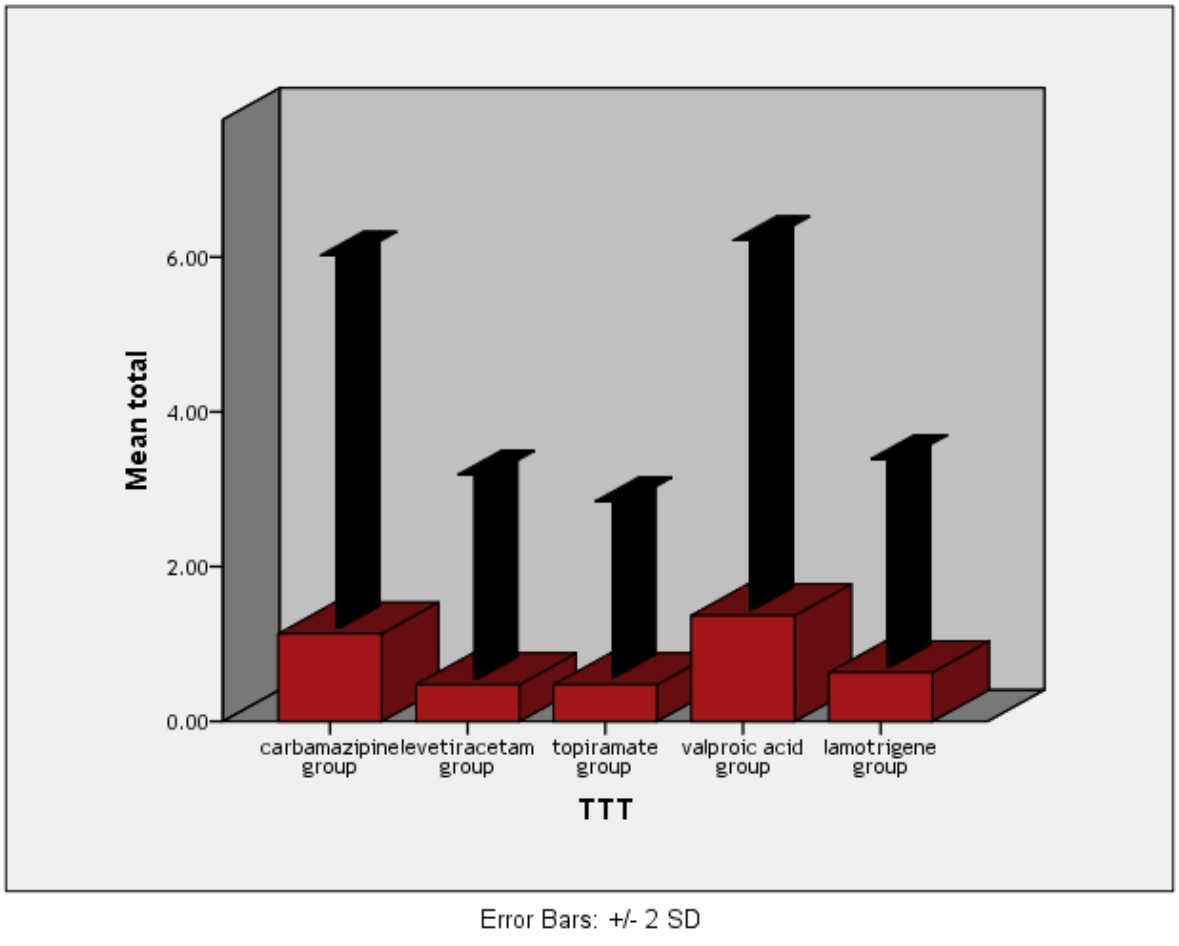

Figure (2): Relation with type of treatment distribution among studied group.

Table 5 shows statistically significant increased total seizure frequency after 6 months treatment, and breakthrough state among group shifted to generic name, also most of cases on carbamazepine (88.2%) shifted to generic name due to high cost of drug and 47.1% of shifted group shifted back due to increased seizure frequency, a statistically significant increased total seizure frequency after 6 months treatment among group shifted to generic name, also most of cases on drug (63.6%) shifted to generic name due to high cost of drug and 36.4% of cases shifted due to drug unavailability, while only 27.3% of shifted group shifted back due to increased seizure frequency, a statistically significant increased total seizure frequency after 6 months treatment and breakthrough status among group shifted to generic name, also more than half of cases on drug (56.2%) shifted to generic name due to high cost of drug and 37.5% of cases shifted due to drug unavailability, while 43.8% of shifted group shifted back due to intolerability of drug and increased seizure frequency, a statistically significant increased baseline seizure, total seizure frequency after 6 months treatment, status epilepticus rate and breakthrough status among group shifted to generic name, also most of cases on drug (69.2%) shifted to generic name due to high cost of drug and 23.1% of cases shifted due to drug unavailability, while 46.2% of shifted group shifted back due to intolerability of drug and increased seizure frequency, statistically significant increased baseline seizure, total seizure frequency after 6 months treatment, status epilepticus rate and breakthrough status among group shifted to generic name, also most of cases on drug (62.5%) shifted to generic name due to high cost of drug and 37.5% of cases shifted due to drug unavailability, while 50% of shifted group shifted back due to intolerability of drug and increased seizure frequency.

Table (5): Association Relation between patient characteristics and shift to generic name among studied cases on carbamazepine, levetiracetam, topiramate, valproic acid, and lamotrigine drugs

Carbamazepine					
Variable		**Shifted group N=17**	**Not shifted group N=59**	**t-test/ MW***	**P-value**
Age		**44.1 ± 7.71**	**44.2 ± 7.63**	**0.061**	**0.955 NS**
Duration		**16 (6-31)**	**14 (6-31)**	**0.92***	**0.36 NS**
Baseline seizure		**2 (1-5)**	**1 (1-3)**	**1.62***	**0.12 S**
Total seizure after 6 months		**0 (0-11)**	**0 (0-6)**	**2.39***	**0.01 S**
		N (%)	**N (%)**	**X^2 test**	
Sex	**Male**	**13 (76.5%)**	**43 (72.9%)**	**0.09**	**0.77 NS**
	Female	**4 (23.5%)**	**16 (27.1%)**		
Cause of shift	**High cost**	**15 (88.2%)**	**------**		
	Unspecific cause	**2 (11.8%)**	**------**	**-----**	**------**
Shift back		**8 (47.1%)**	**-----**	**----**	**-----**
Status epilepticus		**2 (11.8%)**	**3 (5.1%)**	**Fisher**	**0.31 NS**
Breakthrough status		**8 (47.1%)**	**10 (16.9%)**	**6.61**	**0.01 S**
Levetiracetam					
Variable		**Shifted group N=11**	**Not shifted group N=65**	**t-test/ MW***	**P-value**
Age		**40.1 ± 12.1**	**36.8 ± 12.13**	**0.961**	**0.35 NS**
Duration		**14 (3-26)**	**7 (1-38)**	**1.82***	**0.06 NS**
Baseline seizure		**1 (1-4)**	**1 (1-3)**	**0.462***	**0.62 NS**
Total seizure after 6 months		**0 (0-8)**	**0 (0-6)**	**2.11***	**0.04 S**
		N (%)	**N (%)**	**X^2 test**	
Sex	**Male**	**9 (81.8%)**	**46 (70.8%)**	**0.59**	**0.45 NS**
	Female	**2 (18.2%)**	**19 (29.2%)**		
Cause of shift	**High cost**	**7 (63.6%)**	**------**		
	Unavailability	**4 (36.4%)**	**------**	**-----**	**------**
Shift back		**3 (27.3%)**	**-----**	**----**	**-----**
Status epilepticus		**2 (18.2%)**	**2 (3.1%)**	**Fisher**	**0.091 NS**
Breakthrough status		**4 (36.4%)**	**8 (12.3%)**	**Fisher**	**0.061 NS**
Topiramate					

Carbamazepine					
Variable		Shifted group N=17	Not shifted group N=59	t-test/ MW*	P-value
Variable		Shifted group N=16	Not shifted group N=60	t-test/ MW*	P-value
Age		41.9 ± 10.11	38.3 ± 9.13	0.61	0.35 NS
Duration		15 (9-30)	15 (3-30)	0.62*	0.56 NS
Baseline seizure		1 (1-2)	1 (1-2)	1.92*	0.202 NS
Total seizure after 6 months		0 (0-5)	0 (0-4)	2.61*	0.004 S
		N (%)	N (%)	X^2 test	
Sex	Male	11 (68.8%)	40 (66.7%)	0.025	0.88 NS
	Female	5 (31.2%)	20 (33.3%)		
Cause of shift	High cost	9 (56.2%)	------	-----	------
	Unavailability	6 (37.5%)	------		
	Unspecific cause	1 (6.2%)	-----		
Shift back		7 (43.8%)	-----	----	-----
Status epilepticus		2 (12.5%)	1 (1.7%)	Fisher	0.11 NS
Breakthrough status		6 (37.5%)	6 (10.0%)	7.18	0.006 S
Valproic acid					
Variable		Shifted group N=13	Not shifted group N=63	t-test/ MW*	P-value
Age		41.9 ± 10.11	38.3 ± 9.13	0.61	0.35 NS
Duration		12 (3-29)	12 (1-29)	0.62*	0.56 NS
Baseline seizure		2 (1-5)	1 (1-4)	1.92*	0.02 S
Total seizure after 6 months		4 (0-10)	0 (0-6)	3.69*	<0.001 HS
		N (%)	N (%)	X^2 test	
Sex	Male	10 (76.9%)	45 (71.4%)	0.15	0.68 NS
	Female	3 (23.1%)	18 (28.6%)		
Cause of shift	High cost	9 (69.2%)	------	-----	------
	Unavailability	3 (23.1%)	------		
	Unspecific cause	1 (7.7%)	-----		
Shift back		6 (46.2%)	-----	----	-----
Status epilepticus		6 (46.2%)	4 (6.3%)	Fisher	0.001 S
Breakthrough status		9 (69.2%)	13 (20.6%)	Fisher	0.001 S
Lamotrigine					
Variable		Shifted group N=16	Not shifted group N=60	t-test/ MW*	P-value
Age		39.5 ± 8.11	36.3 ± 7.59	1.56	0.15 NS
Duration		15 (2-30)	13.5 (2030)	0.89*	0.36 NS
Baseline seizure		1 (1-4)	1 (1-2)	2.92*	0.006 S
Total seizure after 6 months		5 (0-7)	0 (0-4)	2.96*	0.003 S
		N (%)	N (%)	X^2 test	
Sex	Male	14 (87.5%)	45 (75.0%)	Fisher	0.56 NS
	Female	2 (12.5%)	15 (25.0%)		
Cause of shift	High cost	10 (62.5%)	------	-----	------
	Unavailability	6 (37.5%)	------		
Shift back		8 (50.0%)	-----	----	-----
Status epilepticus		3 (18.8%)	1 (1.7%)	Fisher	0.03 S
Breakthrough status		8 (50.0%)	10 (16.7%)	7.77	0.02 S

Table 6 shows failure (breakthrough seizures) significantly associated with higher age, longer duration of disease, male and generic shift.

Table (6): Association with breakthrough seizures distribution among studied groups.

Variable			No	Failure	t/ MW/ X^2	P-value
Age			**37.70±9.55**	**41.58±11.12**	**3.14**	**0.002***
Duration			**12.73±2.55**	**17.31±3.84**	**4.65**	**0.00****
Sex	**Male**	**N**	**207**	**69**	**8.99**	**0.003***
		%	**69.5%**	**84.1%**		
	Female	**N**	**91**	**13**		
		%	**30.5%**	**15.9%**		
Shift	**No**	**N**	**260**	**47**	**37.12**	**0.00****
		%	**87.2%**	**57.3%**		
	Yes	**N**	**38**	**35**		
		%	**12.8%**	**42.7%**		
Total		**N**	**298**	**82**	---------	
		%	**100.0%**	**100.0%**		

Table 7 shows group had Shift to generic significantly higher in total number of seizures.

Table (7): Association between number of seizures and shift.

Variable	No	Shift to generic	MW	P-value
Total number of seizures	**0 (0-6)**	**2 (0-11)**	**4.85**	**0.00****

DISCUSSION

One of the most prevalent neurological illnesses is epilepsy, whose prevalence peaks around ages 5 to 9 and over 80, showing a bimodal distribution. Epilepsy increases with age and is more prevalent in women and low-income nations [(5)].

Most of the more recent ASMs as well as all traditional ASMs currently have generic versions accessible. The active medicinal components used in branded goods are also present in generic versions of ASMs. If the maximum plasma drug concentration (Cmax) ratios of both products fall within the range of 80-125% with 90 percent confidence intervals, the bioequivalence of generic medicines is authorized [(3)].

As regard demographic data of the studied patients in our study. We found that 72.6% of the patients were males and 27.4% females. Age in the study population ranged from 18 to 62 with mean 38.54 (SD 10.02) years.

Our results were supported by **Tharavichitkun *et al.*** [(6)] they sought to compare the effectiveness and tolerability of generic ASMs to their brand-name counterparts in a typical clinical scenario. The analysis covered 75 patients. All patients ranged in age from 9 to 84, with a mean age of 40.3 (SD 17.9) years, and 53.3% of them were female.

In the current study, we found that the mean duration of treatment with ASMs among study population ranged from 1 to 38 years with mean 13.72 (SD 6.52) years. Moreover, only 19.2% of our study population had shift to generic name drugs. Switching from brand-name to generic formulations has raised concerns among our study population regarding loss of seizure control and occurrence of adverse events. Factors affecting the patients' decisions to switch to generic ASMs were unavailability of brand medications and/ or financial issues.

Also, **Bosak *et al.*** [(7)] the safety of having epileptic patients transfer from brand-name to generic levetiracetam (LEV). According to this study, therapy lasted anywhere between 2 and 4 years, with 3 years serving as the median. Only 6%of the 159 patients who received LEV treatment and 151 participants who were made to convert to generic LEV within a month experienced breakthrough seizure.

In our study we found that the number of seizures was significantly higher among Valproic acid group in 3rd, 6th month, and seizures are significantly higher among Valproic acid and Carbamazepine groups in total during study period. Also, we found that Valproic acid group associated with higher breakthrough seizures than other groups but statistically not significant.

In the present study we found that 6.8% of the studied group was admitted to hospitals due to status epilepticus and 21.6% had breakthrough seizures.

These results were in line with **Niyongere *et al.*** [(8)] they wanted to identify and measure obstacles to the generic replacement of anti-seizure drugs. It was most generally believed that generic replacement would be difficult for valproic acid.

Regarding breakthrough seizures in our patients switched from brand to generic ASMs, we found that breakthrough seizures was significantly associated with higher age (p=0.002), longer duration of disease (p=0.00) and male sex. The elderly has an increased risk of seizures because of kindling phenomenon, polytherapy and multiple comorbidities.

We were in agreement with **Chaluvadi *et al.*** [(9)] revealed that when sex, seizure type, and treatment characteristics were adjusted, age in individuals with epilepsy was substantially linked with switchback (increased seizure frequency or adverse effects) (p< 0.05).

In the current study, regarding Carbamazepine group, we found statistically significant increase in total seizure frequency and breakthrough seizures after 6 months treatment among group shifted to generics (p=0.01). Regarding levetiracetam, there was statistically significant increased total seizure frequency after 6 months treatment among group shifted to generics (p=0.04).

Our results were in agreement with **Beng Hoong *et al.*** [10] they wanted to assess the safety of generic levetiracetam substitution for brand-name levetiracetam. According to their findings, switching reportedly makes seizures more severe (p value 0.031 and 0.05 respectively).

Our results agree with **Lang *et al.*** [11] who revealed a link between changing the manufacturer of anti-seizure drugs and an increased risk of seizure recurrence.

On the other hand, our results did not match with **Kesselheim *et al.*** [12] they evaluated data comparing brand-name and generic ASMs and performed a meta-analysis to see if there was any proof that the brand-name version was better in keeping seizure control. Their meta-analysis revealed no distinction in seizure control between generic and branded medications in randomized control trials.

Also, these results are in disagreement with **Tiamkao *et al.*** [13] who claimed that generic ASMs were equally effective, safe, and safe as the original ASMs. According to their research, generic ASMs may provide better seizure management than original ASMs.

Trimboli *et al.* [14] showed that patients with focal or generalized epilepsy did not have a change in seizure frequency when moving from an ASM's brand to a generic version and a sizable portion of this group continued to be seizure-free over time. Additionally, there were no significant differences in adverse effects or the emergence of new side effects following the changeover from LEV brand to generic.

The current study has several limitations. We did not perform blood monitoring for serum ASMs levels, as the relationship between ASMs serum concentration and its clinical effect has not been fully established. Also, we did not study patients who were switched between different generic manufacturers due to availability of several generics for some brand ASMs especially, Levetiracetam.

In conclusion, there is a potential association between the risk of breakthrough seizures and switching from brand to generic ASMs. Generic substitution of Valproic acid was significantly associated with high risk of breakthrough seizures. This is because generic ASMs may not be bioequivalent to that of brand formulations and therefore, generic drug substitution may cause therapeutic failure and increased risk of adverse effects. The risk of these seizures was the highest among the elderly populations. Therefore, it would be unwise to switch patients with epilepsy from brand to generic ASMs.

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