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Comparative Antiseizure Activities of Some Branded and Generic Antiepileptic Drugs in a Nigerian City

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ABSTRACT

Branded antiepileptic drugs (AEDs) are expensive, and in developing countries, cheaper generic equivalents may be used interchangeably. Therefore, this study aimed to compare the antiseizure activities of some available branded and generic AEDs in mice. The physicochemical properties of four generic and branded AEDs (carbamazepine, CAB; sodium valproate, SVP; phenytoin, PHY, and phenobarbitone, PHB) were determined according to pharmacopoeial methods. The organoleptic properties, tablet hardness and thickness of the samples were also assessed. The anticonvulsant effect of AEDs was determined using maximal electroshock (MES) and pentylenetetrazole (PTZ) induced seizure. The samples of AEDs showed uniformly comparable organoleptic properties. The active moiety content for all the samples fell within the acceptable ranges stipulated in the official compendia. A significant statistical difference ($p \leq 0.05$) in disintegration time existed between two generic formulations of PHB, PHB01 (4.62±1.17 min), and PHB02 (1.40±0.26 min). Similarly, a significant statistical difference ($p \leq 0.05$) in hardness (10.40±0.15 kgF vs 5.61±0.03 kgF) and disintegration time (4.65±0.49 min vs 0.64±0.30 min) was observed between the two brands of CAB (CAB02 and CAB03 respectively). No significant statistical difference exists in mean recovery time between control (5.70±0.72 min) and treatment groups (CAB01, 6.50±0.65 min) in the MEST. In the PTZ test, there was a significant ($p \leq 0.001$) difference in the mean onset of clonic spasm between control (10.03±0.75 min) and PHB, PHB01 (17.50±0.99 min) 30 min post-treatment. In conclusion, no significant variation in the physicochemical and antiseizure activity of branded and generic formulations of AEDs was observed.

Keywords: *Antiepileptic drugs, Branded and generic drugs, Seizure, Bauchi, Nigeria*

INTRODUCTION

In 2015, epilepsy was recognized as a significant global health concern, especially in developing African countries, including Nigeria, during the 68th World Health Assembly held in Geneva (Olubunmi 2006; Fodjo 2020). Epilepsy is one chronic neurological condition affecting people of all ages globally, with peak incidence rates in children and adults over 60 (WHO 2019). The International League Against Epilepsy (ILAE) defined it as a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition (Fisher 2014). Epilepsy has a worldwide distribution (Beghi et al. 2019), and it is a significant cause of disability worldwide (Femi et al. 2019). According to the ROW Foundation (2020), 80% of the 65 million people with

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epilepsy worldwide live in low- and middle-income countries (ROW Foundation 2020). Its prevalence is high in developing countries, especially in Latin America and several African countries, notably Liberia, Nigeria, and the United Republic of Tanzania, compared with the prevalence rates of between 4 and 6 per 1000, which have been reported among Caucasians (Olubunmi 2006). In Nigeria, the prevalence of epilepsy varied remarkably from one place to another, with figures obtained from population-based studies ranging from 3.1 - 37 per 1,000 (Femi et al. 2019).

Antiepileptic drugs (AEDs) are the cornerstone for treating epileptic seizures (Landmark et al. 2020). Worldwide (including Nigeria), different drug products (both branded and generic) are available for optimum management (Hanssens et al. 2002). Therefore, the success of a long treatment period for a patient afflicted with a disease depends mainly on carefully selecting a suitable antiepileptic regimen, optimum dosing, and patient compliance (Buck et al. 1997). There are many brands of the same drug in the market due to the proliferation of pharmaceutical manufacturing industries. The availability of different brands of the same drug puts most prescribers in a severe dilemma for their patients (Nwodo et al. 2007). Generic medicines have the same quality, efficacy, and safety properties as originator (branded) drugs while being available at more affordable prices (Fadare et al. 2016). Furthermore, generic drugs are typically 20-90% cheaper than originator equivalents, and their use has increased in recent years, primarily due to cost-saving measures in healthcare provision (Dunne et al. 2013). For example, U.S. generic drugs have saved the U.S. healthcare system $1.67 trillion in the last decade, generating $253 billion in savings in 2016 alone. Medicare savings amounted to $77 billion ($1,883 per enrollee), and Medicaid savings to $37.9 billion ($512 per enrollee). About 3.9 billion generic prescriptions were also generated (AAM 2017).

Generally, AEDs are affordable at low cost. Still, long-term prescription refills with a low-cost generic formulation may lead to substantial drug-budget savings, especially when moving from branded high-cost to low-cost generic formulations. It has been cited in the literature that patients with a higher preference for brand-name drugs who are limited to generic options may have reduced compliance, which could lead to even higher healthcare costs and other adverse outcomes over time (Keenum et al. 2012). To this effect, the World Health Organization (WHO) advocated using generic prescriptions to contain the cost of drugs, particularly in low-income countries. Here, multisource generic products could be used interchangeably provided they met the regulatory requirements (WHO 2014). The Nigerian National Standard Treatment Guidelines reaffirmed the use of generic prescriptions. Therefore, generic products are expected to be pharmaceutically and therapeutically equivalent to a reference-listed drug (WHO 2006a; EMA 2010; CDER 2015).

To the best of our knowledge, there is a lack of studies on the comparative effects of different formulations of AEDs available in various drug outlets in developing countries. Therefore, this study aimed to perform a comparative evaluation of the antiseizure activities of some commercially available branded and generic AEDs in mice. The findings of this study will serve as a basis for prescribing the available AEDs to epileptic patients. It is noteworthy that therapeutic equivalence for a multi-generic drug is essential to prevent seizure relapse or intoxication when switching to or among generic AEDs (Holtkamp and Theodore 2018).

MATERIALS AND METHODS

Ethical Clearance and Collection of Drug Samples

The study was approved by the Animal and Ethics Research Committee of the Department of Pharmacology and Therapeutics, Ahmadu Bello University Zaria, Nigeria, with a reference number (DAC/IW-OT/1-12). Branded and generic formulations of carbamazepine (200 mg tablets), sodium valproate (200 mg tablets), and phenobarbitone (30 mg) were randomly bought from registered pharmacy outlets in Bauchi, north-eastern Nigeria. The samples were coded and stored in their original packets before the study at the recommended conditions specified by their respective manufacturers' manuals. Branded (reference) drugs were also coded with registered superscripts.

Experimental Animals Handling

Swiss mice (18-30 g) of either sex were obtained from the Department of Pharmacology and Therapeutics, Ahmadu Bello University Zaria, Nigeria, and day-old ranger Cockerels (19-36 g) were obtained from the National Animal Production Research Institute (NAPRI) Shika, Zaria. The animals were kept and maintained in well-ventilated, ambient laboratory conditions of temperature and humidity and were allowed food and water *ad libitum*.

Table 1: Identity of the Drug Samples used in the Study

Drug	Brand code	Country of origin
Phenytoin (200 mg)	PHY01®	India
	PHY02	India
Phenobarbitone sodium (30 mg)	PHB01®	UK
	PHB02	Nigeria
Sodium valproate (200 mg)	SVP01®	UK
	SVP02	India
Carbamazepine (200 mg)	CAB01®	Italy
	CAB02	Malaysia
	CAB03	China

®Refers to the branded (reference) drug

Preliminary Comparative Organoleptic Studies of the Selected Antiepileptic Drugs

The organoleptic properties (colour, odour and taste) of the samples were assessed to ascertain their conformity with the branded sample AEDs (Borgherini 2003).

Physical Properties

Different samples of tablets were subjected to various physical tests. These included tablet thickness and diameter (using digital vernier caliper), hardness (using Monsanto hand hardness tester), and disintegration time (using Eureka disintegration test apparatus), as described in British Pharmacopoeia (British Pharmacopoeia 2002).

Chemical Assay

Phenobarbitone sodium, carbamazepine, and sodium valproate tablets were assayed according to the British Pharmacopoeial method described in the monograph of the respective samples (British Pharmacopoeia 2002). Phenytoin sodium was assayed according to the WHO method (WHO 2006b).

Maximal Electroshock (MEST) Test in Chicks

The method of Swinyard and Kupferberg (1985) was used for this study. A total of 320 day-old chicks were randomly divided into six groups having ten for the different dose levels per body weight of the animals and two post-treatment periods (15 and 30 min) for each of the selected drug samples.

A control group was set up and was given 0.9% normal saline 10 ml/kg intraperitoneally (i.p). For phenytoin (PHY01 and PHY02), the first, second, and third groups were injected with 5, 10, and 20 mg/kg, respectively, of the selected drug samples via the i.p route.

After 15 and 30 min, respectively, maximum electroshock was administered to induce a seizure in the chicks using the Ugo Basile electroconvulsive machine (Model 7801) connected to a stabilizer with corneal electrodes attached to the upper eyelids of the chicks. The current, shock duration, frequency, and pulse width were set and maintained at 90 mA, 0.8 s, 100 pulses/s, and 0.6 ms, respectively. The time of recovery of convulsed chicks was recorded, and the percentage of convulsed animals was calculated.

The same procedures were applied for CAB (CAB01, CAB02 and CAB03), each at dose levels of 10, 20, and 40 mg/kg respectively. The ability to prevent tonic-clonic hind limb extension or reduction in the recovery period was regarded as an indication of the effectiveness of the drug sample.

Pentylenetetrazole (PTZ)-Induced Seizure in Mice

The method described by (Swinyard et al. 1989) was employed in this study. The sample size was calculated based on the assumption that a minimum of six mice is required per group to give good statistical power for analysis (Ya'u et al. 2015). There were two drugs (valproate and phenobarbitone) with two brands each, and three graded doses of each drug were required in a group at two post-treatment periods of 15 and 30 min. Thus, 25 groups of six mice per group were needed. Therefore the total number of animals used was 150. The Mice of both sexes were randomly divided into six groups, each for the different dose levels per body weight of the animals and two post-treatment periods for each of the selected drug samples; sodium valproate and sodium phenobarbitone. A control group of six mice were also set up and was given 10ml/kg of 0.9% normal saline via the intraperitoneal route (i.p). For sodium valproate (SVP01) and (SVP02), the first, second, and third groups were administered 50, 100, and 200 mg/kg of the prepared stock solution of the drug samples. At 15 and 30 min, respectively, the mice were injected with 85 mg/kg pentylenetetrazole subcutaneously (s.c.) and observed over 30 min. The absence of an episodic clonic spasm of at least five seconds indicates the drug's effectiveness in abolishing pentylenetetrazole's effect on seizure threshold. The presence or absence of threshold seizures, the mean onset of convulsion, quantal protection and percentage protection, number of episodes, and time to death were observed in all the animals. The same procedure was applied for the two drug samples of phenobarbitone sodium (available only as generic preparation) with doses of 7.5, 15, and 30 mg/kg.

Table 2: Organoleptic Properties of the Selected Branded and Generic Drug Formulations

Brand code	Taste	Colour	Odour
PHY01®	Bitter	Crystalline white	Odourless
PHY02	Bitter	Crystalline white	Odourless
PHB01®	Tasteless	White	Odourless
PHB02	Tasteless	White	Odourless
SVP01®	Tasteless	Purple	Odourless
SVP02	Tasteless	Pink	Odourless
CAB01®	Tasteless	Crystalline white	Odourless
CAB02	Tasteless	Crystalline white	Odourless
CAB03	Tasteless	Crystalline white	Odourless

Statistical Analyses

Statistical analyses were performed using one-way analysis of variance (ANOVA) on mean recovery time and the onset of spasm, followed by Dunnett's post hoc test. Levels of statistical significance were considered at $p<0.05$. All statistical analyses were conducted using Statistical Application Package for Social Science, SPSS version 19.0 (SPSS Inc., Chicago, IL). The results obtained were expressed as descriptive statistics.

RESULTS

Different brands of various AEDs were collected and coded, as shown in Table 1. Concerning organoleptic properties, both branded and generic drug samples used in this study showed some remarkable similarities concerning taste, colour and odour. Phenytoin (PHY01® and PHY02) were crystalline white, odourless and bitter. Phenobarbitone (PHB01® and PHB02) were tasteless, odourless and white. However, sodium valproate; SVP01® was purple; while SVP02 was pink in colour, and both were tasteless and odourless (Table 2).

Table 3: Physicochemical Properties of the Drug Samples

Brand code	Hardness (Kgf)	Diameter (mm)	Thickness (mm)	Disintegration time (min)	% of active moiety
PHY01®	-	-	-	-	101.49
PHY02	-	-	-	-	104.38
PHB01®	5.39 ± 0.00	5.46 ± 0.00	2.59 ± 0.00	4.62 ± 1.17	102.05
PHB02	5.40 ± 0.06	6.31 ± 0.01	2.58 ± 0.02	1.40 ± 0.26*	96.54
SVP01®	11.08 ± 0.10	9.35 ± 0.01	4.33 ± 0.02	11.31 ± 0.61	100.26
SVP02	10.96 ± 0.04	9.71 ± 0.01	4.63 ± 0.01	11.25 ± 0.83	100.39
CAB01®	5.61 ± 0.03	8.80 ± 0.04	3.60 ± 0.04	0.64 ± 0.30	105.00
CAB02	10.40 ± 0.19*	9.97 ± 0.01	2.96 ± 0.00	4.65 ± 0.49*	104.00
CAB03	5.44 ± 0.04	9.97 ± 0.00	3.90 ± 0.03	1.12 ± 0.16	103.33

Data presented as Mean ± SEM, p < 0.05 student t-test; n=6. Official specification (% of active moiety) in the individual tablet monogram; PHY: 90-110 (IP 2003), PHB: 95-105 (BP 2002), SVP: 98.5-101 (BP 2002) and CAB: 90-110 (BP 2002). * - Significantly different between branded and generic AED at p<0.05; Phenytoin capsules were used and therefore hardness, diameter, thickness, and disintegration time were not assessed.

Regarding the physicochemical properties of the samples, similarities in tablet hardness, diameter and thickness between the two generic and branded formulations of carbamazepine (CAB01®, CAB02 and CAB03) were observed. Similarly, the two generic formulations of sodium valproate (SVP01® and SVP02) exhibited similarity in tablet hardness, diameter and thickness, and disintegration time. On the other hand, the generic formulations of phenobarbitone (PHB01® and PHB02) only exhibited similarities in tablet hardness, diameter and thickness (Table 3).

Table 4: Effect of Carbamazepine on Maximal Electroshock-Induced Seizure in Chicks

Drug (mg/kg)	Quantal protection	% protection	Mean recovery time (min)
Control	0/10	0.00	5.70 ± 0.72
CAB01®			
10a	0/10	0.00	6.90 ± 0.89
20a	1/10	10.00	6.22 ±1.46
40a	4/10	40.00	6.50 ± 0.65
CAB01®			
10b	1/10	10.00	11.00 ± 3.72
20b	4/10	40.00	13.00 ± 1.97
40b	7/10	70.00	4.00 ±1.00
CAB03			
10a	1/10	10.00	7.67 ± 1.17
20a	8/10	80.00	5.00 ± 1.00
40a	10/10	100.00	0.00 ± 0.00

Data presented as Mean ± SEM and percentage; a = 15 min and b = 30 min post-treatment periods; Data not significantly different (p>0.05) between branded and generic AED

Also, an assay for the determination of active moiety content of the drug samples used in this work has shown that all the drug samples contained an active moiety that falls within the ranges stipulated by official compendia, BP 2002 and IP 2003. Regarding the physicochemical properties of the samples, similarities in tablet hardness, diameter and thickness between the two generic and branded formulations of carbamazepine (CAB01®, CAB02 and CAB03) were observed. Similarly, the two generic formulations of sodium valproate (SVP01® and SVP02) exhibited similarity in hardness, diameter and thickness as well as disintegration time. On the other hand, the generic formulations of phenobarbitone (PHB01® and PHB02) only exhibited similarities in tablet hardness, diameter and thickness (Table 3). Also, an assay for the determination of active moiety content of the drug samples used in this work has shown that all the drug samples contained an active moiety that falls within the ranges stipulated by official compendia, BP 2002 and IP 2003 (Table 3).

The three formulations of carbamazepine used in the study showed dose-dependent protection against seizure induced by maximal electroshock. The highest protection (100%) was observed at 40 mg/kg dose for CAB03 between 15 and 30 min, and CAB02 at 30 min after i.p administration of the drugs. Seventy percent protection was obtained at 40 mg/kg for CAB01®, 30 min after i.p. administration of the drug, while 20 mg/kg of CAB03 offer 80 and 90% protection between 15 and 30 min, respectively after i.p. administration. CAB02 at 20 mg/kg 30 min after i.p. administration produced 100% protection. However, all the samples of carbamazepine showed no significant statistical effect on mean recovery time in the treatment groups compared with the control group (p>0.05) (Table 4).

The two generic formulations of phenytoin (PHY01® and PHY02) used in the study showed dose-dependent protection against seizure induced by maximal electroshock. The highest protection of 90% was obtained at 20 mg/kg 30 min after i.p. administration of PHY02 generic phenytoin. In comparison, PHY01® generic phenytoin at the same dose gave 70% protection 30 min after i.p. administration and no protection was observed in the control group. At 20 mg/kg 15 min after i.p. administration of PHY01® generic phenytoin, 50% protection was obtained, while at the same dose and time, 40% protection was observed for PHY02 phenytoin. Only samples PHY01 and PHY02, both at 5 mg/kg, showed a significant

statistical effect on mean recovery time in the treatment groups compared relative to the control group after 15 min post-treatment (Table 5).

Table 5: Effect of Different Generic Formulations of Phenytoin on Maximal Electroshock Test in Chicks

Drug (mg/kg)	Quantal protection	% protection	Mean recovery time (min)
Control	0/10	0.00	6.50 ± 0.90
PHY01®			
5a	1/10	0.00	11.10 ± 0.59**
10a	2/10	20.00	7.12 ± 1.44
20a	5/10	50.00	3.80 ± 0.80
PHY01®			
5b	0/10	0.00	5.40 ± 0.86
10b	0/10	0.00	9.10 ± 1.48
20b	7/10	70.00	7.00 ± 2.08
PHY02			
5a	0/10	0.00	10.10 ± 0.74*
10a	0/10	10.00	6.33 ± 0.83
20a	4/10	40.00	4.67 ± 0.95
PHY02			
5b	1/10	10.00	7.89 ± 0.94
10b	2/10	20.00	6.13 ± 0.55
20b	9/10	90.00	8.00 ± 0.00

Data presented as Mean ± SEM and percentage; a = 15 min and b = 30 min post-treatment periods; **, * - Significantly different between branded and generic AED at p<0.01 and 0.05 respectively

The branded (SVP01®) and generic (SVP02) formulations of sodium valproate used in the study produced dose-dependent protection against PTZ-induced seizure. The highest protection (100%) was offered by SVP01® 100 mg/kg 15 and 30 min before subcutaneous (s.c.) administration of PTZ. SVP02 at 100 and 200 mg/kg also provided 100% protection at 15 min before s.c. injection of PTZ. SVP02 at 100 and 200 mg/kg offered 83.33% protection, while SVP01® at 100 and 200 mg provided 10 and 33.33%, respectively, administered 30 min before s.c. injection of PTZ. Only samples SV01 and SV02, at a dose of 50 mg/kg after 15 min post-treatment, and also SV02 at both respective doses of 50 and 200 mg/kg after 30 min post-treatment, showed a significant statistical difference in mean recovery time in the treatment groups when compared with the control group (Table 6).

The two generic formulations of phenobarbitone sodium (PHB01® and PHB02) used in the study produced dose-dependent protection against PTZ-induced seizure. A 100% protection was offered by PHB01® at 15 mg/kg, 15 min before subcutaneous injection of PTZ, while PHB02 offered 66.67% protection at 15 mg/kg and 15 min before s.c. administration of PTZ. PHB02 offered 100% protection at 30 mg/kg, 15 and 30 min before s.c. administration of PTZ. PHB01® at 7.5 mg/kg and 15 min before s.c. injection of PTZ offered 83.33% protection, while PHB02 had 66.67% protection 15 min before s.c. injection of PTZ. There was no protection observed in the control group. Finally, samples PHB01 at a dose of 7.5 mg/kg after 15 min post-treatment and PHB02 at doses of 7.5 and 15 mg/kg and after 30 min post-treatment showed a significant statistical difference in mean recovery time in the treatment groups when compared with the control group (Table 7).

DISCUSSION

The assay for determining the active moiety content of the drug samples used in this work has shown that they contained active moiety that fell within the acceptable ranges in the official compendia (British Pharmacopoeia 2002; WHO 2006b). The active moiety in the different drug samples of AEDs in this study was responsible for the observed dose-dependent pharmacological activities: These activities were measured in terms of percentage protection, reduction in the mean recovery, and the increased onset of tonic-clonic hind limb extension, which are the parameters of the efficacy of compounds with antiepileptic activity. Organoleptic assessment of the studied drug samples has revealed a comparative similarity concerning taste, odour, and colour, except for sodium valproate samples where SVP01 was purple and SVP02 was pink.

Table 6: Effect of Different Branded and Generic Formulation of Sodium Valproate on Pentylenetetrazole-induced Seizure in Mice

Drug (mg/kg)	Quantal protection	% protection	Mean onset of clonic spasm (min)
Control	0/6	0.00	11.67 ± 0.61
SVP01®			
50a	2/6	33.33	22.50 ± 2.22*
100a	6/6	100.00	0.00 ± 0.00
200a	3/6	50.00	7.67 ± 2.19
SVP01®			
50b	2/6	33.33	20.00 ± 5.57
100b	6/6	100.00	0.00 ± 0. 00
200b	2/6	33.33	8.70 ± 1.01
SVP02			
50a	3/6	50.00	17.67 ± 2.19*
100a	6/6	100.00	0.00 ± 0.00
200a	6/6	100.00	0.00 ± 0.00
SVP02			
50b	3/6	50.00	10.67 ± 3.76*
100b	5/6	83.33	18.00 ± 0.00
200b	5/6	83.33	29.00 ± 0.00**

Data presented as Mean ± SEM, and percentage; a = 15 min and b = 30 min post-treatment periods; **, * - Significantly different between branded and generic AED at p<0.01 and 0.05 respectively

Assessment of the physical characteristics of the drug samples showed inter-formulation variations concerning disintegration time, tablet diameter and tablet thickness: These might be attributed to the difference in formulation techniques employed during manufacturing, such as granulation method, com-

pressional force, type(s) of excipients used, and the physicochemical properties of the active and inactive ingredients (Paesschen et al. 2009). There was a correlation between the tablet hardness, disintegration time, and pharmacological activity: The lesser the hardness of the drug the faster the disintegration and dissolution of the active moiety, and the higher the bioavailability. Hence, the better the pharmacological effect of the drug. On the other hand, the harder the tablet, the slower the disintegration time and the lower the bioavailability, hence the slower onset of pharmacological activity (Bhowmik et al. 2010).

Table 7: Effect of Two Generic Formulations of Phenobarbitone Sodium on Pentylenetetrazole-induced Seizure in Mice

Drug (mg/kg)	Quantal protection	% protection	Mean on set of clonic spasm (min)
Control	0/6	0.00	10.83 ± 0.75
PHB01®			
7.5a	5/6	83.33	17.50 ± 0.99**
15a	6/6	100.00	0.00 ± 0.00
30a	4/6	66.67	9.50 ± 0.50
PHB01®			
7.5b	0/6	0.00	9.60 ± 1.41
15b	4/6	66.67	9.50 ± 0.50
30b	4/6	66.67	9.50 ± 1.50
PHB02			
7.5a	4/6	66.67	12.00 ± 3.00
15a	4/6	66.67	9.50 ± 0.50
30a	6/6	100.00	0.00 ± 0.00
PHB02			
7.5b	2/6	33.33	16.25 ± 1.80*
15b	2/6	33.33	4.00 ± 0.71**
30b	6/6	100.00	00.00 ± 0.00

Data presented as Mean ± SEM, and percentage; a = 15 min and b = 30 min post-treatment periods; **, * - Significantly different between branded and generic AED at p<0.01 and 0.05 respectively

Different salts of the same active substance can exhibit other chemical and biological properties. Also, excipients in the tablet may not always be considered inactive or inert and can differ from one generic to another and affect the pharmacokinetics of the active substance (Paesschen et al. 2009).

Pentylenetetrazole and MES tests are of significant importance with regard to their application in characterizing epilepsy types (Rogawski and Porter 1990; Kupferberg and Schmutz 1998). These two animal models characteristically describe three types of seizure activities. These were demonstrated by the effect of phenobarbitone sodium and sodium valproate against PTZ-induced seizure, which correlates with anti-absence activity, and the development of carbamazepine and phenytoin against electrically induced seizures which represents activity against generalized tonic-clonic and partial seizures (Kupferberg and Schmutz 1998).

Gamma-amino butyric acid (GABA), a major inhibitory brain neurotransmitter, is reported to underlie epilepsy (Amabeoku et al. 1998). The enhancement of GABAergic neurotransmission is reported to antagonize seizures, while the inhibition of the neurotransmission promotes seizures (Leonard 2003).

The protection of chicks against electrically induced seizures by carbamazepine and phenytoin of different generic and brand-named formulations demonstrated that the drugs had comparable anti-seizure activity. This is revealed by statistical inference and may be employed interchangeably in the management of generalized tonic-clonic and partial seizures.

Despite this comparative anti-seizure activity of the various brand-named and generic formulations of AEDs, bioequivalent studies for generic preparation are usually carried out in a small population as a single dose administration and often in low doses. These studies do not parallel the clinical reality of patients often on multiple medications, occasionally fasting, sometimes elderly, pregnant women, children, and disabled patients.

Under generic prescribing, if there are multiple generic manufacturers of an agent, patients receive a different generic formulation each time they present a prescription. When patients are switched between different generic formulations, there is potential for greater variation in drug pharmacokinetics than from brand-to-generic or generic-to-brand formulation (Nuwer et al. 1990). Therefore, switching should be done with due care and precautions to minimize possible adverse consequences that may exacerbate the condition of patients (Jankovic and Ristic 2015).

Fluctuations in serum concentration of AEDs of the different generic formulations may compromise patient safety and increase the risk of seizures, particularly when the dose has been titrated to be just enough to control seizures while avoiding side effects (Borgherini 2003). An issued guideline from the UK National Institute for Clinical Excellence states that "changing the formulation or brand of AEDs is not recommended because different formulations may vary in their bioavailability or pharmacokinetic profile and thus, increased potential for reduced bioactivity or excessive side effect. Once an effective AED treatment regimen is identified for a patient, continuity of treatment is important to maintain seizure control (National Institute for Health and Care Excellence 2012).

The issue of generic prescribing and dispensing is thus not just about economic benefit and generic versus branded product supply but also about uncontrolled switching between generic-generic, brand-generic, brand-brand, or vice-versa. The potential clinical impact of multiple generic switching on a patient with epilepsy is not known, and, it is difficult to predict which patient with epilepsy may have problems with a switch in a formulation. As already stated, loss of seizure control can impact the patient's quality

of life, as well as clinical and financial implications for the primary and secondary healthcare system.

Conclusion

The study demonstrated a slightly significant variation in the physicochemical and anticonvulsant properties of branded and generic formulations of the AEDs studied. Thus, generic and branded products for the respective formulations may be used interchangeably. The widespread multi-source generic products in Nigeria makes it imperative for the country's pharmacovigilance reporting and post-market surveillance systems, which should be strengthened to help identify therapeutic inequivalence among the different generic formulations that may endanger the lives of patients.

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Conflict of Interest
None declared.

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Authors Contribution
JY and AS conceptualized the work, obtained the resources, developed the methodology and collected data on the animal studies. Besides, JY conducted the data analysis and assisted with the first draft of the manuscript. SA and MAU performed the physicochemical analysis. In addition, SA had a lead role in drafting the article, revision and editing. NMD and IA handled the supervision, validation and visualization. Finally, NMD performed critical revision of the manuscript for intellectual content.

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