**Adverse effects of carbamazepine monotherapy among patients in Nigeria – a pilot study and implications**

Adedunni Olusanya[1], Olayinka Ogunleye[2], *Brian Godman[3,4,5], Joseph Fadare[6], Mustafa Danesi[7]

[1]Department of Pharmacology, Therapeutics and Toxicology, College of Medicine, University of Lagos, Nigeria. Email: dedunolusanya@gmail.com
[2]Department of Pharmacology, College of Medicine, Lagos State University, Ikeja, Lagos, Nigeria. Email: yinkabode@yahoo.com
[3]Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institutet, Karolinska, Karolinska University Hospital Huddings, SESE-141 86, Stockholm, Sweden. Email: Brian.Godman@ki.se
[4]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK. Email: Brian.Godman@strath.ac.uk
[5]Health Economics, University of Liverpool Management School, Liverpool University, Liverpool, UK
[6]Department of Pharmacology and Therapeutics College of Medicine, Ekiti state University, Ado-Ekiti, Nigeria. Email: jofadare@gmail.com
[7]Department of Medicine, College of Medicine, University of Lagos, Nigeria. Email: mustaphadanesi@yahoo.com

*Author for correspondence. Division of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden. Email: Brian.Godman@ki.se. Telephone + 46 8 58581068. Fax + 46 8 59581070 and Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom. Email: brian.godman@strath.ac.uk. Telephone: 0141 548 3825. Fax: 0141 552 2562

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**Abstract.**
*Background and aims*: Antiepileptic drugs do cause adverse effects, affecting quality of life, adherence and seizures. Consequently, need to study this among Nigerian patients. *Methods*: Descriptive cross-sectional study assessing the extent of adverse effects with carbamazepine monotherapy and potential factors. *Results:* 54 patients (64.3 %) reported no adverse effects, while 30 did. Commonest adverse effects were memory problems followed by headaches, restlessness, tiredness and depression. Adverse effects were significantly higher in females, with females with low educational levels having significantly higher rates. Dose, co-medications, seizure control and comorbid conditions did not significantly affect adverse effects. *Conclusions:* Perception of adverse effects was common in patients on carbamazepine monotherapy, more common in women than men. Educational status was important in women.

**Introduction**
Epilepsy is a chronic neurological condition that affects between 65 to 70million people worldwide [1, 2], with drug therapy the mainstay of the treatment. It is estimated that 70% of patients will respond to the medicines prescribed whilst the remainder will need surgery and other forms of therapy to achieve seizure control [2, 3, 4].

Antiepileptic drugs (AEDs) are known to have a high propensity for adverse effects (AEs) because of their mechanism of action and their metabolic pathway, with up to 80% of patients experiencing an adverse event [5-8]. AEs are contributors to poor drug compliance, which can be as high as 30% to 50% of adults living with epilepsy, low quality of life and drop outs from drug therapy [4,5,9]. AEs include neuropsychiatric, gastrointestinal, dermatological, endocrine and haematological side-effects. Neuropsychiatric adverse events include memory impairment, headaches, drowsiness, difficulty in concentration and fatigue [6, 8,10,11].

The presence of AEs may require dose adjustments and, in severe cases, total discontinuation of the offending medicines and their replacement with other medicines that possess their own unique adverse effect profile [2].

The medicines used for treating epilepsy are broadly grouped into first and second generation and recently third generation. Whilst the second and third generation medicines have a relatively lower rate of AEs profile, their cost, availability and unclear AEs profile in pregnancy limits their use [12,13,14].

Of the first generation AEDs, carbamazepine is the most commonly used. It is indicated as a first line in patients with a partial seizure and also found to useful in generalized epilepsies. It is inexpensive, easily available and with relatively less adverse effect profile compared to other AEDs especially in women of child bearing age [2, 15]. This is particularly important for Nigeria where an appreciable percentage of the costs of medicines are paid for out-of pocket [16]. This is similar to a number of other African countries.

Apart from specific antiepileptic agents, reports of adverse events have been shown to be higher with higher doses during the introduction of a new AED, in polytherapy, and when there is a change in dosage [17]. The presence of comorbid neuropsychiatric disorders have also been linked to the presence of adverse effects [18]. Other factors such as age, sex, the presence of other comorbidities and use of other drugs apart from AEDS may also contribute to AEs [10].

The extent of AEs with AEDs have been assessed based on patient's reports or measured using standard questionnaires. Questionnaires have been found to be more sensitive to assess reports of adverse effects compared to patient's reports [18, 19].

Most published papers have studied the reports of adverse effects in populations outside of Africa, especially among Western countries. This is a concern as the pharmaogenetic profile of patients in Africa may be different from many Western countries [20]. The studies undertaken in Africa have addressed the use of antiepileptic medications on specific domains like cognition and included patients on polytherapy with widely varying periods of drug treatment and also lack the comprehensiveness of this study. Furthermore, there is paucity of data regarding the assessment of adverse effects using standard questionnaires and incorporating factors such as the use of herbal medicines, which is more common on African countries than Western countries.

Consequently, the objective of this study is to assess the reports of adverse effects in a cohort of Nigerian patients on carbamazepine monotherapy for the treatment of epilepsy using a standardized questionnaire, and determine the contributory factors to reports of adverse events. This can subsequently be extended to other research facilities across Nigeria as well as African countries given differences in genetic make-ups across Africa [20, 21].

## Methods

### *Study site*

This study was a cross-sectional observational study conducted at the Neurology outpatient clinic of the Lagos University Teaching Hospital, Idi-araba, Lagos (LUTH). This site was chosen as Lagos is the economic capital city of Nigeria, and this hospital is a leading teaching hospital in Nigeria. Consequently, can provide a robust basis for assessing the adverse effects of carbamazepine in routine clinical care in Africa.

### *Ethical consideration*

Ethical approval was obtained from the Health Research and Ethics committee of LUTH. A written informed consent was also obtained from all study participants prior to inclusion in the study.

### *Study population*

The study population consisted of 84 consecutively consenting patients. The inclusion criteria were a diagnosis of epilepsy, which is defined as the occurrence of at least two unprovoked seizures occurring more than 24 hours apart according to the International League against Epilepsy (ILAE) definition [22], use of carbamazepine monotherapy for at least 9 months and consenting patients. The patients were assessed after a minimum of 9 months in order to assess adverse effects after a relatively prolonged period of carbamazepine use. The period was also long enough to assess the efficacy of carbamazepine in preventing seizures [23]. Patients who were on polytherapy and not on carbamazepine, pregnant women and non-consenting patients were excluded from this study.

Adverse effect profiles were assessed using Liverpool Adverse Events Profile (LAEP). A score of 1 was given for no symptoms for a particular attribute such as tiredness, restlessness, headache or blurred vision, whilst a score of 2-4 was ascribed for each adverse symptom based on the frequency of symptoms from rarely to always/ often [7]. We chose the Liverpool Adverse Events profile methodology as it is an internationally recognised way to assess the level of adverse effects with medicines used to treat patients with epilepsy [7, 24].

***Methodology***

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A standard questionnaire was administered to all study participants to document demographic data, clinical characteristic of seizure, duration of symptoms, frequency of symptoms and compliance. Adverse effects were evaluated using the 21 item LAEP questionnaire. The total dose of carbamazepine in the past 24 hours was also documented. The date of last epileptic seizure was obtained historically and corroborated by documentation from case records as necessary.

A detailed physical examination including a detailed neurological examination was performed on all study participants to identify any neurological deficits.

Seizure control was classified as fully controlled for individuals who are seizure free for at least six months following the commencement of drug therapy, partially controlled for patients having a reduction in seizure frequency following the commencement of drug therapy and uncontrolled for patients whose seizure frequency has not changed or worsened since onset of drug therapy. Six months is the minimum period to assess drug efficacy in controlling seizures [23]. This is why a minimum cut-off of 9 months was chosen for this study.

***Documentation of data and statistical analysis***

Information from the patients' history and physical examination was recorded directly into the standard proforma by the investigator and transferred into Microsoft Excel spreadsheet.

Data generated from the study was analysed using Statistical Package for Social Sciences (SPSS) software version 21. Data distribution was investigated using the Kolmogorov-Smirnov and Shapiro-Wilk normality tests for appropriate statistical analysis. The baseline demographic and clinical characteristics were analysed using descriptive statistics such as mean, standard deviation (SD), median, range and proportions. Mann Witney U test, Chi-square, Kruskal Wallis test, Spearman's correlation analysis and multiple regression analysis were used to relate adverse effect profile to other variables. P value less than or equal to 0.05 was considered statistically significant.

Tables, figures and chart were constructed using Microsoft word and excel 2013 and the Statistical Package for Social Sciences (SPSS) software version 21.

**Results**

84 patients were included in the study.

***Demography and clinical characteristics***

The demography and clinical characteristics of study participants are shown in the Tables 1 and 2. The population was made up of 47(56%) males and 37(44%) females. The age range was 14-71 years with a mean 34.5 ± 16.5 years.

Focal seizures were more common, accounting for 57(67.9%) of the population studied while generalized seizures occurred in 27 patients (32.1%).

Based on aetiology, 12 patients (14.3%) had a positive family history of epilepsy, 27 (32.1%) had a possible symptomatic/secondary seizures while there was no identifiable cause in 45 (53.6%) of the patients. The risk factors identified for symptomatic epilepsy in this study included; traumatic brain injury in 7 patients (8.3%), childhood febrile seizures 6 (7.1%), low birth weight and prematurity 4 (4.8%), post stroke 3 (3.6%), difficult delivery 3 (3.6%), neuro-cutaneous syndrome (tuberose sclerosis, and neurofibromatosis) 2 (2.3%) and neonatal jaundice 1 (1.2%).

The most common finding on neurological examination of the patients was cognitive impairment, which was present in 6 (7.1 %) of the participants, neurological deficit post stroke which was present in 3 (3.6%) patients and congenital deafness present in 1 patient (1.2%).

Comorbidities were present in 22 (24.2%) patients. They include hypertension 8 in 8 (9.5%), tension type headache in 13 (8.3%), stroke in 3 (3.6%) and cervical spondylosis in 1 (1.2%). The three patients with stroke also had hypertension.

The duration of seizures ranged from 1 to 26years, with the mean duration being 7.26±6.49 years. Duration of treatment ranged from 9 months to 25years, with a mean of 5.92±5.74 years. Doses of carbamazepine used in the study ranged from 200-1000mg per day, with a mean of 528.57 ±21.59mg per day.

Out of the 84 patients, 49(58.3%) patients had attained 6 months seizure freedom while 35(41.7%) had partially controlled seizures. There was no participant with uncontrolled seizures.

Table 1. Demographic data of the study participants (N=84)

| **Variables** | **Frequency (n)** | **Percentage (%)** |
|---|---|---|
| Gender | | |
| Male | 47 | 56.0 |
| Female | 37 | 44.0 |
| | | |
| Age group (years) | | |
| < 20 | 16 | 19.0 |
| 20-29 | 24 | 28.6 |
| 30-39 | 17 | 20.2 |
| 40-49 | 11 | 13.1 |
| 50-59 | 5 | 6.0 |
| >59 | 11 | 13.1 |
| | | |
| Marital status | | |
| Single | 49 | 58.3 |
| Married | 35 | 41.7 |
| | | |
| Education Level | | |
| Primary | 9 | 10.7 |
| Secondary | 40 | 47.6 |
| Tertiary | 35 | 41.7 |
| | | |
| Employment status | | |
| Student | 26 | 31.0 |
| Employed | 40 | 47.6 |
| Unemployed/Retired | 18 | 21.4 |

Table 2. Clinical characteristics of study participants (n=84)

| Variable | Frequency (n) | Percentage (%) |
|---|---|---|
| Seizure type | | |
| Focal | 57 | 67.9 |
| Generalized | 27 | 32.1 |
| Presumed aetiology | | |
| Presumed genetic/idiopathic | 12 | 14.3 |
| Secondary/symptomatic | 27 | 32.1 |
| Unknown/cryptogenic | 45 | 53.6 |
| Neurological examination | | |
| Normal | 74 | 88.1 |
| Abnormal | 10 | 11.9 |
| Age at seizure onset | | |
| Childhood onset | 33 | 39.0 |
| Adult onset | 51 | 61.0 |
| Seizure control | | |
| Partial control | 35 | 41.7 |
| Full control | 49 | 58.3 |
| Comorbidities present* | | |
| No comorbidities | 62 | 73.9 |
| Tension type headache | 13 | 15.5 |
| Hypertension | 8 | 9.5 |
| Stroke | 3 | 3.6 |
| Spondylotic neuropathy | 1 | 1.2 |
| Medicine prescribed | | |
| Tegretol | 78 | 92.8 |
| Zeptol | 5 | 6.0 |
| Carzepin | 1 | 1.2 |
| Herbal drugs and other medications* | | |
| Herbal drugs | 14 | 16.7 |
| Antihypertensive drugs | 8 | 9.5 |
| Amitriptyline | 7 | 8.3 |
| Aspirin | 7 | 8.3 |
| Multivitamin | 3 | 3.6 |
| Propanolol | 2 | 2.3 |
| Daily dose in mg (carbamazepine) | | |
| 200 | 1 | 1.19 |
| 400 | 53 | 63.1 |
| 600 | 10 | 11.9 |
| 800 | 15 | 17.9 |
| 1000 | 5 | 6.0 |

*Some patients had more than one comorbidity.

***Adverse effects in study participants.***

The study showed that 54 patients (64.3%) reported no AEs while 30 patients (35.7%) reported AEs. (Table 3). Twenty three (27.5%) patients reported a single adverse effect while 4 (4.8%) reported 2 adverse effects. The maximal number of adverse effects occurring together in an individual patient was 3, which affected 3 (3.6%) patients.

The median LAEP score was 21 (IQR=21-22) at the 95% confidence interval (CI) (Table 3). The highest score was 28. The majority of patients (54 - 64.3 %) had a score of 21, which represented no adverse effects, and 19 (22. 6%) had a score of 22 which represented one adverse effect. Six (7.2%) patients had a score of 23, 2 (2.4%) had a score of 24 while scores of 25, 27 and 28 occurred in one patient respectively (1.2%). Scores of 23 -28 represented patients with either more severe adverse effects or patients with more than one adverse effect.

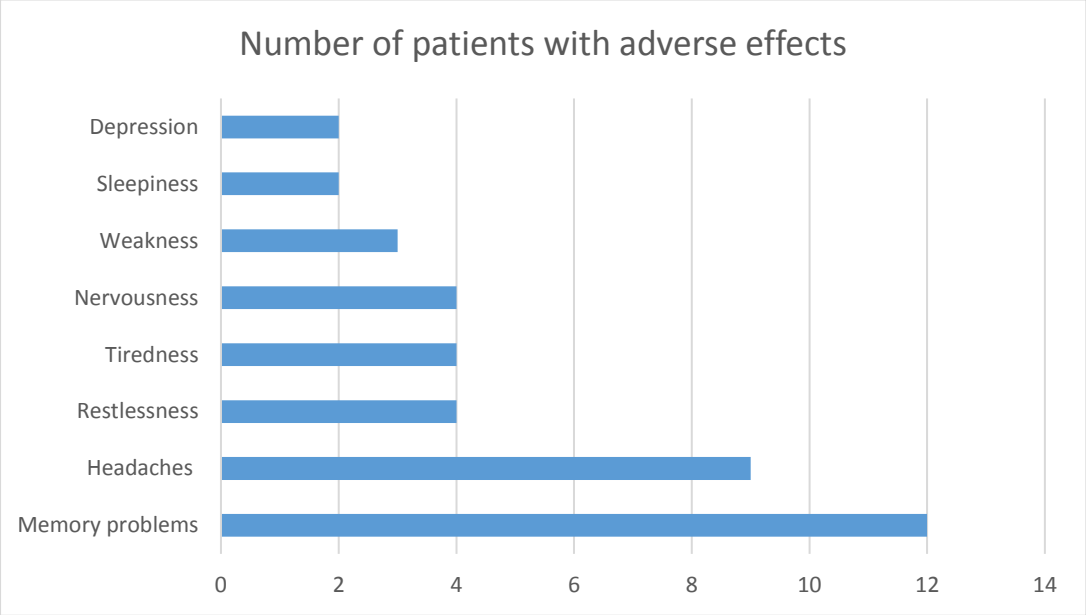
The most common AE was memory problems, which was present in 12 (14.3%) patients, closely followed by headaches in 9 (10.7%) patients (Table 3, Figure 1). Other adverse effects included restlessness in 4 (4.8%), tiredness in 4 (4.8%), depression in 4 (4.8%), nervousness in 4 (4.8%), weakness and sleepiness 3 (3.6%).

In patients with more than one adverse effect, headaches, memory impairment and restlessness each had a frequency of three and were the most frequently reported adverse effects. Headache was present in all the patients who reported 3 adverse effects, weakness and restlessness occurred together in two patients while all the other adverse effects were randomly distributed among the patients who had 2 or 3 adverse effects.

Table 3. Adverse effects in study participant.

| Adverse Effect | Number of patients (N) | Percentage (%) |
|---|---|---|
| No adverse effects | 54 | 64.3 |
| Adverse effects present | 30 | 35.7 |
| 1 adverse effect | 23 | 27.5 |
| 2 adverse effects | 4 | 4.8 |
| 3 adverse effects | 3 | 3.6 |
| LAEP Scores | | |
| 21 | 54 | 64.3 |
| 22 | 19 | 22.6 |
| 23 | 6 | 7.2 |
| 24 | 2 | 2.4 |
| 25 | 1 | 1.2 |
| 27 | 1 | 1.2 |
| 28 | 1 | 1.2 |
| Adverse effects | | |
| Headaches, memory, tiredness | 1 | 1.2 |
| Headaches, sleepiness and tiredness | 1 | 1.2 |
| Restlessness, headaches, nervousness | 1 | 1.2 |
| Headaches and memory | 1 | 1.2 |
| Memory and nervousness | 1 | 1.2 |
| Weakness and restlessness | 2 | 2.4 |
| Memory | 9 | 10.7 |
| Headaches | 5 | 6.0 |
| Depression | 2 | 2.4 |
| Nervousness | 2 | 2.4 |
| Tiredness | 2 | 2.4 |
| Weakness | 1 | 1.2 |
| Sleepiness | 1 | 1.2 |
| Restlessness | 1 | 1.2 |

Figure 1 – Number of patients with adverse events




**NB** Some patients had more than one adverse effect.

***Independent predictors of adverse effects.***
Mann Whitney U nonparametric test, Kruskal Wallis nonparametric test and Spearman's correlation analysis were used to test the association between Liverpool adverse effects score and other variables.

The results showed that adverse effects were more common in females which is statistically significant (P =0.012) (Table 4). Further analysis showed that women who were less educated reported significantly higher rates of adverse effects. (P= 0.03). (Table 5).

Table 4 . Relationship between adverse effect and characteristics of participants (N=84)

| Variables | N | Mean ± SD | Median | Range | p value |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 47 | 21.4±0.8 | 21 | 21-24 | 0.012* |
| Female | 37 | 22.0±1.6 | 22 | 21-28 | |
| Other drugs | | | | | |
| Yes | 21` | 21.6±1.0 | 21 | 21-24 | 0.602* |
| No | 63 | 21.7±1.0 | 21 | 21-28 | |
| Herbal drugs | | | | | |
| Yes | 14 | 21.3±0.4 | 21 | 21-22 | 0.622* |
| No | 70 | 21.7± 1.3 | 21 | 21-28 | |
| Seizure control | | | | | |
| Partial control | 35 | 21.7±1.3 | 21 | 21-28 | 0.422* |
| Full control | 49 | 21.7±1.2 | 21 | 21-27 | |
| Comorbidities | | | | | |
| Yes | 22 | 21.64±1.5 | 21 | 21-28 | 0.943* |
| No | 62 | 21.7±1.1 | 21 | 21-27 | |
| Brand | | | | | |
| Tegretol | 78 | 21.7± 1.2 | 21 | 21-28 | 0.624** |
| Zeptol | 5 | 21.6 ± 0.5 | 22 | 21-22 | |
| Carzepin | 1 | 23.0± 0.0 | 23 | 23-23 | |

Table 5 Relationship between educational status and reports of adverse effects in females (N=37)

| Variable | AE present | No AE | Total | $X^2$ | P-value |
|---|---|---|---|---|---|
| Educational level | | | | | |
| Primary and Secondary | 7 | 14 | 21 | 4.56 | 0.033 |
| Tertiary | 11 | 5 | 16 | | |

*Mann Whitney U nonparametric test.
**Kruskal Wallis test nonparametric test.

The extent of comedication use, herbal drug use, presence of comorbid conditions, seizure control and brand of carbamazepine used did not affect reports of AEs. Similarly, age and drug dose did not show any significant relationship with reports of AEs (Tables 5 and 6).

Table 6. Spearman's correlation analysis between LAEP score and other variables (N=84)

| Variable | rs | p-value |
|---|---|---|
| Dose | -0.141 | 0.199 |
| Age | 0.104 | 0.901 |

**Discussion.**

This study showed that perception of adverse effects was common (occurred in one of three patients) on carbamazepine monotherapy for the treatment of epilepsy. Adverse reports were significantly higher in women compared to men, and women who were also less educated were more likely to have adverse events (Tables 4 and 5).

The rates of AEs in this study is similar to that reported by Suresh et al [25], and Fadare et al [10], who reported adverse effects rates of 36.6% and 37.6% respectively, although both studies used non-structured questionnaires. Other studies using adverse effect questionnaires have reported rates between 60-78% [6, 26,27].

Reports of adverse effects are expected to be higher when questionnaires are used compared to unstructured interview [24, 28]. However, this study showed that only 30 (35.7%) of patients with epilepsy had adverse effects, which is relatively lower than that expected considering a structured questionnaire was used. The differences in the various studies may be explained by the drug formulations used and differences in the population studied. Some of the studies included patients on immediate release carbamazepine, while all the patients in our study were on controlled release carbamazepine. A Cochrane analysis showed that patients on immediate release carbamazepine were more likely to have higher rates of adverse effects compared to those on controlled release, though not statistically significant [29].

The characteristics of patients studied in publications is also an important contributor to differences in reported AE rates. Some studies included patients on carbamazepine therapy for a shorter period of time, polytherapy with sometimes with up to 3 AEDs, monotherapy with different AEDs and some included patients with drug resistant epilepsy [6, 25-27,29]. An earlier study in Nigeria, which reported adverse effects rates of 37.6%, had patients on therapy for a shorter duration of treatment, people on controlled release and immediate release formulations of carbamazepine and also included patients on polytherapy [10]. The patients in this study had been on carbamazepine monotherapy for a minimum of nine months. Consequently, they remained on the drug for a relatively longer period of time compared to other studies. This time period may have been long enough for patients with intolerable adverse effects to have dropped out of therapy, changed to another medication or developed tolerance to the presence of adverse effects. As a result, potentially underreporting the level of adverse effects seen with carbamazepine.

Although there is an overlap in the adverse effect, their frequency and distribution vary in different studies. The adverse effects reported across various studies include memory impairment, headaches, somnolence, restless and sleepiness, drowsiness, difficulty in concentrating, nervousness, memory problems and fatigue [8,10,11,19].

In this study, the commonest adverse event reported was memory impairment followed by headaches, and others including somnolence, restless and sleepiness (Table 3, Figure 1). The high rates of memory impairment are similar to reports by Suresh et al and Eddy et al [25, 30]. Whereas a study carried out in the south-south region of Nigeria did not report significant memory impairment in patients on AEDs [31].

The adverse effects reported in this study were mainly neuropsychiatric manifestations. There were no cutaneous manifestation such as rashes that may suggest anticonvulsant hypersensitivity. Anticonvulsant hypersensitivity syndrome are immune mediated and genetic based reactions that occur following the use of aromatic anticonvulsants such as carbamazepine, phenytoin, phenobarbibital or lamotrigine [32]. Though they are rare, they are life threatening. Consequently, there is a need to identify these reactions and withdraw the offending drug early. Other features of this condition include fever, lymphadenopathy, malaise and pharyngitis. Symptoms usually develop within a few weeks of commencement of antiepileptic drugs and could occur as late as 3 months post treatment [32]. The absence of features suggestive of anticonvulsant hypersensitivity syndrome in this study may be explained by the fact that the patients have been on carbamazepine for a relatively long period.

In this study, the rates of adverse effects were found to be higher in women with lower educational attainment. Higher rates of adverse events in females have also been reported in other studies [7, 10, 33]. Hormonal influence may play a role in metabolism of antiepileptic; consequently, predisposing to reports of adverse effects. Further studies need to be done to compare the pharmacokinetics of carbamazepine between males and females and across countries to further elucidate on this phenomenon.

Most studies have evaluated anti-epileptic related adverse effects retrospectively. Poor educational attainment may be due to memory impairment or associated stigma of the disease. This in itself may be primarily due to epilepsy especially syndromic ones. [34]. Again because a baseline cognitive assessment was not done pre-treatment, it might be difficult to blame it all on AEDs. Age, dose, duration of treatment, the presence of comorbidities and use of co-prescribed medications did not significantly affect the reports of AEs.

This study involved a relatively uniform population, so findings in this study are relatively easier to interpret. To the best of our knowledge, this is the first study that evaluated the presence of adverse effects in epilepsy using a structured questionnaire among Nigerian patients with epilepsy. The higher reports of adverse effects in females in this study may be as a result of relatively poor educational status of women which may affect the perception of AEs. Hormonal differences may also contribute to this. Further studies are needed to assess this and a prospective study will be able to distinguish between AEs and worsening of comorbid conditions as a result of AED use.

***Limitations***

The study involved a relatively small number of patients. We accept a larger sample would have been more appropriate in order to better characterize the occurrence of adverse effects. However, the population studied was fairly homogeneous. The study also reported AE occurring with longer term rather than shorter term use of carbamazepine because patients were assessed after nine months of therapy. However, we believe our findings are valid. We are now planning a prospective study to better understand the situation as there can be overlap in comorbid symptoms and reports of AE.

**Conclusion.**

This pilot study assessing the reports of AEs retrospectively in patients on carbamazepine monotherapy for the treatment of epilepsy found that reports of AEs are common in patients on carbamazepine monotherapy, similar to other published studies. Adverse effects were more common in women and mainly affected the neurological system.

The assessment of AEs should be incorporated in the routine evaluation of patients with epilepsy.

Building on this, a prospective study assessing the presence of AEs on a larger sample size is planned to better understand and characterize the nature of the side-effects with carbamazepine and its associations.

**Ethical conduct of research**

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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**Executive Summary**

- Antiepileptic drugs have a high propensity to cause adverse effects because of their mechanism of action and metabolism through the cytochrome p450 pathway
- The presence of adverse effects is a major determinant to the quality of life of patients living with epilepsy and may contribute to drug adherence and ultimately to seizure control
- Carbamazepine is the most commonly used anti-epileptic drug (AED) in Nigeria as it is indicated as a first line agent in partial seizure and also found to useful in generalized epilepsies. It is also inexpensive, easily available and with relatively less adverse effects compared to other AEDs especially in women of child bearing age
- 64.3 % of patients reported no adverse effect with carbamazepine. The commonest adverse effect reported was memory problems in 14.3% and headaches in 10.7%. Other AEs includes restlessness, tiredness, sleepiness and depression
- Adverse effects were significantly higher in females compared to males, and females who had low educational levels also had a significantly higher report of adverse effects
- Dose of carbamazepine, co-medications use including herbals, seizure control and presence of comorbid conditions did not significantly affect reports of adverse effects.
- Further prospective studies are planned to better understand and characterize the nature of the side-effects with carbamazepine and its associations to help with the future care of patients with epilepsy in Nigeria

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