



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

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Aim: Antiepileptic drugs do cause adverse effects, affecting patients' quality of life, adherence and seizures. Consequently, there is a 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. The most common 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. **Conclusion:** Perception of adverse effects was common in patients on carbamazepine monotherapy, more common in women than men. Educational status was important in women.

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Keywords: adverse events • carbamazepine • epilepsy • Nigeria

Epilepsy is a chronic neurological condition that affects between 65 and 70 million 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 while the remainder will need surgery and other forms of therapy to achieve seizure control [2–4].

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 30–50% of adults living with epilepsy, resulting in low quality of life and drop outs from drug therapy [4–5,9]. AEs include neuropsychiatric, gastrointestinal, dermatological, endocrine and hematological 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 AE profile [2].

The medicines used for treating epilepsy are broadly grouped into first and second generation, and recently third generation. While 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 [12–14].

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 be useful in generalized epilepsies. It is inexpensive, easily available and with relatively less AE profile compared with other AEDs especially in women of child-bearing age [2,15]. This is particularly

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Table 1. Demographic data of the study participants.

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

n = 84.

important for Nigeria where an appreciable percentage of the costs of medicines is 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 has also been linked to the presence of AEs [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 extents 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 AEs compared with patient's reports [18,19].

Most published papers have studied the reports of AEs in populations outside of Africa, especially among western countries. This is a concern as the pharmacogenetic profile of patients in Africa may be different from many western countries [20]. The studies undertaken in Africa have addressed the use of antiepilep-

tic medications on specific domains like cognition and included patients on polytherapy with widely varying periods of drug treatment but they lack the comprehensiveness of this study. Furthermore, there is paucity of data regarding the assessment of AEs using standard questionnaires and incorporating factors such as the use of herbal medicines, which is more common in African countries than western countries.

Consequently, the objective of this study is to assess the reports of AEs 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 makeups 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. 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 AEs of carbamazepine in routine clinical care in Africa.

Ethical consideration

Ethical approval was obtained from the Health Research and Ethics committee of Lagos University Teaching Hospital. 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 >24 h apart according to the International League against Epilepsy 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 AEs 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 nonconsenting patients were excluded from this study.

AE 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, while a score of 2–4 was ascribed for each adverse symptom based on the frequency of symptoms from rarely to always/often [7].

Table 2. Clinical characteristics of study participants.		
Variable	Frequency (n)	Percentage (%)
Seizure type:		
– Focal	57	67.9
– Generalized	27	32.1
Presumed etiology:		
– 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
– Zepol	5	6.0
– Carzopin	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
– Propranolol	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. n = 84.		

We chose the LAEP methodology as it is an internationally recognized way to assess the level of AEs with medicines used to treat patients with epilepsy [7,24].

Methodology

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. AEs were evaluated using the 21-item LAEP questionnaire. The total dose of carbamazepine in the past 24 h 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 6 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 & 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 analyzed using Statistical Package for Social Sciences soft-

Table 3. Adverse effects in study participant.

Adverse effect	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

LAEP: Liverpool Adverse Events Profile.

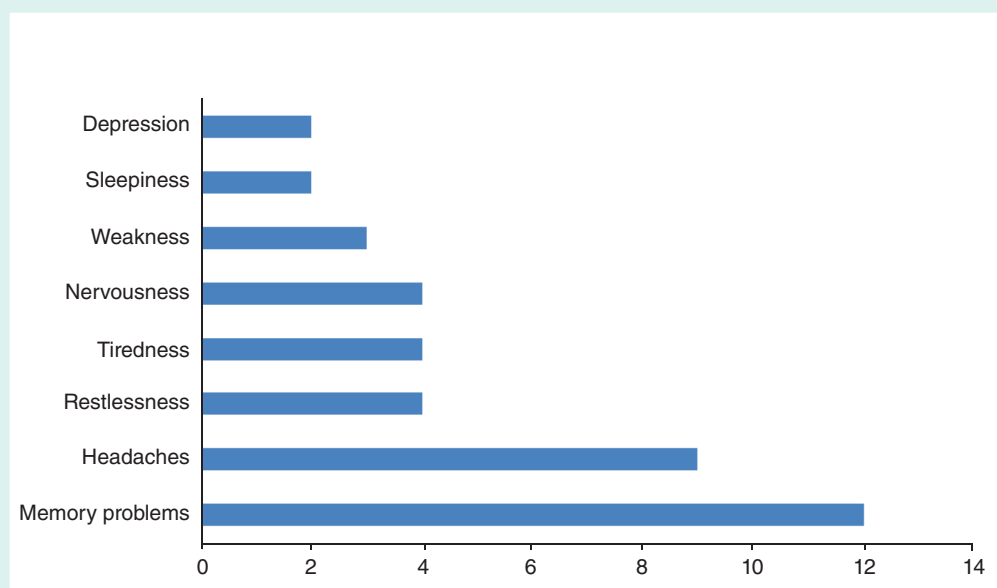


Figure 1. Number of patients with adverse events. Please note some patients had more than one adverse effect.

ware version 21 (IBM Corporation, Armonk, USA). Data distribution was investigated using the Kolmogorov–Smirnov and Shapiro–Wilk normality tests for appropriate statistical analysis. The baseline demographic and clinical characteristics were analyzed using descriptive statistics such as mean, standard deviation, median, range and proportions. Mann–Whitney U test, Chi-square, Kruskal–Wallis test, Spearman’s correlation analysis and multiple regression analysis were used to relate AE profile to other variables. $p \leq 0.05$ was considered statistically significant.

Tables, figures and charts were constructed using Microsoft Word and Excel 2013, and the Statistical Package for Social Sciences software version 21.

Results

In total, 84 patients were included in the study.

Demography & clinical characteristics

The demography and clinical characteristics of study participants are shown in the [Tables 1 & 2](#).

The population was made up of 47 (56%) males and 37 (44%) females. The age range was 14–71 years with 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 the etiology, 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 seven patients (8.3%), childhood febrile seizures six (7.1%), low birth weight and prematurity four (4.8%), post stroke three (3.6%), difficult delivery three (3.6%), neurocutaneous syndrome (tuberous sclerosis and neurofibromatosis) two (2.3%) and neonatal jaundice one (1.2%).

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

Comorbidities were present in 22 (24.2%) patients. They include ([Table 2](#)) tension-type headache in 13 (15.5%), hypertension in eight (9.5%), stroke in 3 (3.6%) and cervical spondylosis in one (1.2%). Three patients with stroke also had hypertension.

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

Out of the 84 patients, 49 (58.3%) patients had attained 6 months seizure freedom while 35 (41.7%)

Table 4. Relationship between adverse effect and characteristics of participants.

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

[†]Mann–Whitney U nonparametric test.
[‡]Kruskal–Wallis test nonparametric test.
n = 84.

had partially controlled seizures. There was no participant with uncontrolled seizures.

AEs 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 AE while four (4.8%) reported two AEs. The maximal number of AEs occurring together in an individual patient was three, which affected three (3.6%) patients.

The median LAEP score was 21 (interquartile range: 21–22) at the 95% CI (Table 3). The highest score was 28. The majority of patients (54; 64.3%) had a score of 21, which represented no AEs, and 19 (22.6%) had a score of 22, which represented one AE. Six (7.2%) patients had a score of 23, two (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 AEs or patients with >1 AE.

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 AEs included restlessness in four (4.8%), tiredness in four (4.8%), depression in four (4.8%), ner-

vousness in four (4.8%), as well as weakness and sleepiness in three (3.6%).

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

Independent predictors of AEs

Mann–Whitney U nonparametric test, Kruskal–Wallis nonparametric test and Spearman's correlation analysis were used to test the association between Liverpool AE score and other variables.

The results showed that AEs 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 AEs ([p = 0.03] Table 5).

The extent of co-medication use, herbal drug use, presence of co-morbid conditions, seizure control and the brand of carbamazepine used did not affect the reports of AEs. Similarly, age and drug dose did not

show any significant relationship with reports of AEs (Tables 5 & 6)

Discussion

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

The rates of AEs in this study are similar to that reported by Suresh *et al.* [25], and Fadare *et al.* [10], who reported AEs rates of 36.6 and 37.6%, respectively, although both studies used nonstructured questionnaires. Other studies using AE questionnaires have reported rates between 60 and 78% [6,26–27].

Reports of AEs are expected to be higher when questionnaires are used compared with unstructured interviews [24,28]. However, this study showed that only 30 (35.7%) patients with epilepsy had AEs, which is 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 populations 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 AEs compared with those on controlled release, though not statistically significant [29].

The characteristics of patients studied in publications are 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 three AEDs, monotherapy with different AEDs and some included patients with drug-resistant epilepsy [6,25–27,29]. An earlier study in Nigeria, which reported AEs 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 9

months. Consequently, they remained on the drug for a relatively longer period of time compared with other studies. This time period may have been long enough for patients with intolerable AEs to have dropped out of therapy, changed to another medication or developed tolerance to the presence of AEs. As a result, potentially under-reporting the level of AEs was seen with carbamazepine.

Although there is an overlap in the AE, their frequency and distribution vary in different studies. The AEs 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 AEs reported in this study were mainly neuropsychiatric manifestations. There were no cutaneous manifestations 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, phenobarbital 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 AEDs 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 AEs 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

Table 5. Relationship between educational status and reports of adverse effects in females.

Educational level	Adverse effect present	No adverse effect	Total	X ²	p-value
Primary and secondary	7	14	21	4.56	0.033
Tertiary	11	5	16		

n = 37.

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

influence may play a role in metabolism of antiepileptic; consequently, predisposing to reports of AEs. 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 antiepileptic-related AEs 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 pretreatment, 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 AEs in epilepsy using a structured questionnaire among Nigerian patients with epilepsy. The higher reports of AEs 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 AEs. 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 9 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. AEs were more common in women and mainly affected the neurological system.

The routine 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.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest

Executive summary

- Antiepileptic drugs have a high propensity to cause adverse effects because of their mechanism of action and metabolism through the CYP450 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 antiepileptic drug in Nigeria as it is indicated as a first-line treatment in patients with partial seizures and also found to be useful in generalized epilepsies. It is also inexpensive, easily available and with relatively less adverse effects compared with other antiepileptic drugs especially in women of child-bearing age.
- No adverse effect with carbamazepine was reported in 64.3% of patients. The commonest adverse effect (AE) reported was memory problems in 14.3% and headaches in 10.7%. Other AEs include restlessness, tiredness, sleepiness and depression.
- Adverse effects were significantly higher in females compared with males, and females who had low educational levels also had a significantly higher level 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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