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Pattern of Adverse Drug Reaction to Antiepileptic Drugs at a Tertiary Hospital in North-Central Nigeria: A Prospective Observational Study

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Authors' contributions

This work was carried out in collaboration between both authors. Author EUE contributed to the concept, design, literature search, data collection and analysis, manuscript preparation, manuscript editing and manuscript review. Author AUC contributed to data collection, manuscript editing and manuscript review. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Epilepsy is a common neurologic condition affecting 0.5-1% of the population. Adverse drug reactions (ADRs) are a major health problem to the individual as well as for the society. There is insufficient awareness and inadequate training on drug safety monitoring among healthcare workers in Nigeria.
Aim: To determine the prevalence and pattern of adverse drug reactions in children on antiepileptic drugs.
Study Design: This was a prospective observational study.
Place and Duration of Study: Pediatric neurology clinic, Jos University Teaching Hospital, Nigeria between January 2011 and December 2015.
Methodology: We recruited consecutive newly diagnosed children with epilepsy that were initiated on antiepileptic drugs. We performed thorough symptom checklist and physical examination before

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initiating antiepileptic drugs. Electroencephalogram, complete blood count, liver function test, and serum electrolytes, urea and creatinine were also done. Patients and their caregivers were counseled on the adverse drug reactions of the drugs being initiated and asked to return to the clinic immediately they observe any of the reactions. Patients were assessed for adverse reactions on each visit. Further laboratory evaluations were done for those with adverse reactions if necessary. Causal relationship between adverse drug reaction and treatment was assessed with the Naranjo Algorithm.

Results: Four hundred and nine patients were initiated on antiepileptic drugs within the study period. Two hundred and twenty-one (54.0%) were on monotherapy while 188 (46.0%) were on polytherapy. The most frequently prescribed drugs were carbamazepine (34.7%), carbamazepine+valproic acid (33.7%) and valproic acid (15.2%). A total of 113 (27.6%) patients had 193 different adverse drug reactions. The commonest adverse drug reactions were sleep disorders (33.7%), skin rash (10.9%), dizziness (7.8%), fatigue (10.7%) and nausea (6.75%). Those on polytherapy were significantly more likely to have adverse drug reactions compared to those on monotherapy (Relative Risk = 1.65, 95% confidence interval 1.20-2.27; P = 0.002).

Conclusion: Adverse drug reactions are common in children on antiepileptic drugs. Pharmacovigilance is very important in children on antiepileptic drugs so that adverse drug reactions can be identified early and managed appropriately.

Keywords: Antiepileptic drugs; adverse drug reaction; pattern; children; North-Central Nigeria.

1. INTRODUCTION

Epilepsy is a disease of the brain defined by any of the following conditions: [1] At least two unprovoked (or reflex) seizures occurring >24 hours apart; [2] one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; [3] diagnosis of an epilepsy syndrome [1]. This definition by the Task Force of the International League Against Epilepsy (ILAE) was adopted by the Executive Committee in December 2013 as an operational definition of epilepsy for purposes of clinical diagnosis. Epilepsy is a common neurologic condition affecting 0.5-1% of the population [2]. Epidemiological studies of epilepsy all over the world have shown higher prevalence rate for developing countries [2]. Cumulative lifetime incidence of epilepsy in children is 3% [3]. The overall aim in treating epilepsy should be complete control of seizures, without causing any untoward reaction due to the medication.

Adverse drug reactions (ADRs) are a major health problem to the individual as well as for society [4]. The World Health Organisation's (WHO) definition of an ADR is ''a response to a drug which is noxious, and unintended, and which occurs at doses normally used in human for prophylaxis, diagnosis or therapy of disease, or for the modification of physiologic function'' [5]. Adverse drug reactions (ADRs) are a major clinical problem in both paediatric and adult medicine. Systematic reviews and meta-analyses of prospective studies of drug surveillance in children have showed that one in 10 children in hospital will experience an ADR [6,7]. Studies in the community suggest that at least one in every 500 children will experience an ADR each year [8]. In 1988, it was identified that the majority of children who receive an antiepileptic drug (AED) as an outpatient will experience an ADR [9]. Since then, however, a significant number of newer AEDs have been introduced, each with its own new ADR profile.

In a large study of fatal suspected ADRs in the UK, AEDs were the group of medicines most likely to be associated with a fatality [10]. Studies in the USA have also suggested that AEDs are associated with a significant number of ADRs [11]. In different studies the prevalence of AEDs side effect varied from 10 to more than 70% [12]. Drugs are the major treatment for seizure, so proper selection and use of antiepileptic drugs (AEDs) can control 60-90% of epileptic patients. Using an appropriate drug to control seizure is related to several factors, such as: accurate diagnosis of seizure type, patient compliance, and drug side effects that play an important role in patient compliance. These side effects vary from mild phenomena, such as drowsiness and mild gastrointestinal and skin symptoms to life threatening side effects, including organs failure and severe skin involvement. For instance, the mortality rate of Stevens-Johnson syndrome, which is a life threatening side effect of AEDs, can be 5-10%.

Older/conventional drugs like phenytoin (PHT), carbamazepine (CBZ), valproic acid (VPA), phenobarbitone (PBT) and Ethosuximide (ETX) are commonly used as first line drugs. They are relatively less expensive than the newer antiepileptics. Drugs like gabapentin, lamotrigine, vigabatrin, topiramate, levetiracetam, tiagabine and zonisamide are the newer antiepileptics. They have lesser adverse effects and have few, if any, drug interactions [13,14]. An unblinded randomised trials comparing Standard and New Antiepileptic Drugs (SANAD) Arm A found that lamotrigine was clinically better than carbamazepine, the standard drug treatment, for time to treatment failure outcomes and is therefore a cost-effective alternative for patients diagnosed with partial onset seizures [15]. The Arm B of the same study however found that valproic acid was better tolerated than topiramate and more efficacious than lamotrigine, and should remain the drug of first choice for many patients with generalised and unclassified epilepsies [16].

The target of epilepsy treatment is to use one AED to fully control the seizure, however patients with multiple seizure types or those with refractory disease may require more than one drug [17]. There is insufficient awareness and inadequate training about drug safety monitoring among healthcare workers in Nigeria. Often, ADRs go unnoticed or are not reported. The aim of the study was to prospectively determine the prevalence and pattern of ADRs in children on AEDs at a tertiary health facility in North-Central Nigeria.

2. MATERIALS AND METHODS

2.1 Background of Study Area

Jos, the capital of Plateau state of Nigeria, is located in the north-central zone of the country. The Jos University Teaching Hospital is one of the three teaching hospitals in the zone. The population of the state was estimated at 3,206,531 in the 2006 census, with the state capital having a population of approximately 900,000 [18]. Children constitute about 45% of the total population.

2.2 Study Site

This study was carried out in the pediatric neurology clinic of Jos university teaching hospital, Jos. The clinic runs every Monday at the pediatric out-patient department (POPD) of the hospital. It receives referrals from the general pediatric out-patient clinic, general out-patient department, other pediatric specialist clinics, surgical units and from other hospitals in different parts of the state and neighbouring states. It also serves as a follow-up clinic for children that were admitted for neurologic diseases in the hospital. It attends to about 40 patients every clinic day, 58% of these patients have epilepsy as the primary disease.

2.3 Study Population

Subjects of the study were new patients aged <18 years attending the pediatric neurology clinic of Jos university teaching hospital, Jos between 2011 and 2015 who were diagnosed with epilepsy and were initiated on AEDs. The diagnosis of epilepsy was made using the International League Against Epilepsy (ILAE) operational definition of epilepsy.

2.4 Study Design

This was a prospective observational study.

2.5 Inclusion Criteria

All newly diagnosed children with epilepsy aged <18 years initiated on AED attending the pediatric neurology clinic of JUTH were recruited for the study.

2.6 Exclusion Criteria

Any child whose parent or guardian did not give consent was excluded from the study.

2.7 Study Procedure

Consecutive patients who met the inclusion criteria that presented at the pediatric neurology clinic from January 2011 to December 2015 were recruited for the study. A thorough symptom checklist and physical examination were done at baseline before initiation of AED. Electroencephalogram (EEG), complete blood count, liver function test, and serum electrolytes, urea and creatinine were done before initiation of AED. Radiological investigations like CT scan and MRI were done if necessary to rule out organic cause for the seizures. Each child was placed on an appropriate AED based on the classification of his/her seizure type. A second AED was added if seizures were not controlled with the maximum dosage of one AED, a third

AED was added if necessary. The maximum dosages of the AEDs used were as follows: CBZ 30 mg/kg/day; VPA 30 mg/kg/day; PBT 5 mg/kg/day; ETX 20 mg/kg/day; LEV 21-30 mg/kg/day depending on the age of the child.

Patients and their caregivers were counseled on the ADRs of the drug being initiated and asked to return to the clinic immediately they observe any of the reactions. All the children on AED were reviewed on each scheduled visit and on any event-triggered visit and assessed for adverse reactions using symptom checklist and physical examination. Further laboratory evaluations were done for those with adverse reactions if necessary. A patient was assessed to be having ADR if he/she developed new symptoms after initiation of AED or has a known side effect of a particular drug after excluding other causes. The WHO guideline was used for the detection, classification and management of AEDs' adverse drug reactions [5]. Causal relationship between ADR and treatment was assessed with the Naranjo Algorithm [19].

2.8 Data Analysis

Data obtained was analyzed using EpiInfo version 7.2. The Kruskal-Wallis test was used for continuous variables while chi-squared test was used to test significance of associations. *P* value <0.05 was considered significant.

2.9 Ethical Consideration

Ethical approval for this study was obtained from the Health Research Ethical Committee (HREC) of Jos University Teaching Hospital. Informed consent was obtained from the parent or guardian of each participant.

3. RESULTS AND DISCUSSION

3.1 Results

Four hundred and nine patients were initiated on AED within the study period. Males were 238 (58.2%) while females were 171 (41.8%). The mean age of the patients was 5.46±3.72 years. One hundred and eighty-one (44.3%) were aged 1-5 years, 136 (33.2%) were aged 6-12 years, 69 (16.9%) were aged <1 year while 23 (5.6%) were aged 13-17 years. Two hundred and twenty-one (54.0%) were on monotherapy, 148 (36.2%) were on dual therapy, 36 (8.8%) were on triple therapy while 4 (1.0%) were on 4 AEDs. In all 221 (54.0%) were on monotherapy while 188 (46.0%) were on polytherapy. The most frequently prescribed drugs were CBZ (34.7%), CBZ+VPA (33.7%) and VPA (15.2%). Table 1 shows the characteristics of the patients.

Table 1. Characteristics of the patients

Characteristics	Total (%)
Sex	
Males	238 (58.2)
Females	171 (41.8)
Age group	
<1year	69 (16.9)
1-5years	181 (44.3)
6-12years	136 (33.2)
13-17years	23 (5.6)
AED Regimen	
Monotherapy	221 (54.0)
Polytherapy	188 (46.0)
AED	
CBZ	142 (34.7)
CBZ+VPA	138 (33.7)
VPA	62 (15.2)
CBZ+VPA+PBT	36 (8.8)
ETX	17 (4.2)
VPA+LEV	10 (2.4)
CBZ+VPA+PBT+LEV	4 (1.0)

AED, antiepileptic drug; CBZ, carbamazepine; VPA, valproic acid; PBT, phenobarbitone; ETX, ethosuximide; LEV, levetiracetam

A total of 113 (27.6%) patients had 193 different ADRs involving different systems. The commonest system/organ affected was central nervous system (CNS) followed by the digestive system (DS) and the skin. The commonest ADRs were sleep disorders (33.7%), skin rash (10.9%), dizziness (7.8%), nausea (6.7%) and fatigue (6.2%). Table 2 shows the different ADRs observed.

One hundred and twenty-eight (66.3%) of the ADRs were probable while 65 (33.7) were possible. AED was discontinued in only 2 cases both as a result of behavioral problem from PBT. AED dosage was adjusted in 28 patients because of sleep disturbance, 17 were on CBZ, 9 were on PBT while 2 were on VPA.

There was no significant difference in the prevalence of ADRs between the different age groups (P = 0.86) and between males and females (P = 0.20). However those on polytherapy were significantly more likely to have ADRs compared to those on monotherapy (Relative Risk = 1.65, 95% confidence interval 1.20-2.27; P = 0.002) (Table 3).

Table 2. Pattern of adverse drug reactions

ADRs^	CBZ	VPA	ETX	PBT	LEV	Total
CNS						
Sleep disorders	38	13	4	6	4	65
Dizziness	5	4	2	2	2	15
Fatigue	3	3	1	3	2	12
Headache	1	4	1	1	2	9
Behavioral problems	3	4	-	2	1	10
Blurring of vision	3	-	-	1	-	4
Skin						
Rash	9	-	-	3	1	21
Alopecia	-	3	-	-		4
Digestive						
Nausea	4	5	2	1	1	13
Vomiting	2	-	-	-	-	2
Abdominal pain	2	2	-	1	1	6
Diarrhea	-	1	-	2	-	3
Elevated ALT levels	1	2	-	2	1	6
Metabolic						
Increased appetite	-	8		-	-	8
Anorexia	-	-	-	-	2	2
Weight gain	-	3	-	-	-	3
Weight loss	-	-	-	-	2	2
Hematologic						
Anemia	2	-	-	-	-	2
Thrombocytopenia	1	1	-	1	-	3
Neutropenia	1	-	-	-	-	1
Others						
Gum hypertrophy	-	1	-	-	-	1
Enuresis	-	1	-	-	-	1

ADRs, adverse drug reactions; CBZ, carbamazepine; VPA, valproic acid; PBT, phenobarbitone; ETX, ethosuximide; LEV, levetiracetam; CNS, central nervous system; ALT, alanine transaminase.
^some children had more than one adverse drug reactions

Table 3. Relationship between age, sex, AED regimen and ADRs

Characteristics	Total (%)	ADRs (%)	No ADRs (%)	*P* value
Age				0.86
<1 year	69 (16.9)	16 (14.2)	53 (17.9)	
1-5 years	181 (44.3)	51 (45.1)	130 (43.9)	
6-12 years	136 (33.2)	39 (34.5)	97 (32.8)	
13-17 years	23 (5.6)	7 (6.2)	16 (5.4)	
Sex				0.20
Female	171 (41.8)	53 (46.9)	118 (39.9)	
Male	238 (58.2)	60 (53.1)	178 (60.1)	
AED Regimen				0.002
Monotherapy	221 (54.0)	47 (41.6)	174 (58.8)	
Polytherapy	188 (46.0)	66 (58.4)	122 (41.2)	

ADRs, adverse drug reactions; AED, antiepileptic drug

3.2 Discussion

This study was carried out to assess the prevalence and pattern of ADRs of AEDs in children with epilepsy in our hospital. The most frequently prescribed AEDs were Carbamazepine (CBZ), valproic acid (VPA) or a combination of the two. The number of patients on polytherapy in our study was higher than what was reported in UK [20] and India [21]. This could be because of the fact that many cases of epilepsy in our community are associated with other neurologic disorders like cerebral palsy and post-meningitic sequelae and that may contribute

to the difficulty in controlling the seizures with one AED. Also some people in Nigeria still believe that epilepsy is as a result of witchcraft or a curse and therefore don't seek medical care early. By the time they come to the hospital the seizure may have become so serious that one AED will not be able to control it. It could also be as a result of the quality of drugs in the country. There are fake drugs in the country and many people buy drugs from sources that are not fully controlled by the regulatory agency.

The prevalence of ADRs in this study (27.6%) is similar to what was reported previously in some studies [20,21] but higher than the 4.7% reported in India [22]. Considering the higher rate of polytherapy in our study one would have expected a higher rate of ADRs. It is possible that some ADRs were not reported and some may have resolved before the patients came for follow up. This is plausible because some of the caregivers of our patients keep buying the drugs from the pharmacy shop and may not come back for follow up for a long time. Also phenytoin (PHT) has been reported to be the drug most implicated in ADRs in children on AED [20,21] and none of our patients received PHT. Many clinicians in Nigeria shy away from the use of PHT because of the high prevalence of ADRs associated with it considering the fact that we don't have facilities for drug level monitoring in the country.

Because CBZ and VPA were the most commonly prescribed drugs, they were responsible for most of the ADRs. However a disproportionate number of patients on PBT (62.5%) had ADRs. Because of the high rate of polytherapy it was not possible to be certain about causal relationship between an AED and an ADR since some AEDs have similar ADRs. AEDs were introduced one by one after reaching the maximum dose of the initial one without achieving complete seizure control. An ADR was attributed to a newly introduced AED if it was not previously present and is a known ADR of that drug. However some AEDs share similar pharmacokinetic and pharmacodynamic properties which may have additive effects and increase the likelihood of ADRs [23,24].

The commonest ADR observed was sleep disturbance. A study in UK [20] reported cognitive/behavioral problems as the commonest ADRs. Other studies in developing countries [21,22,25] have also reported sleep disturbance as the commonest ADR. A higher level of cognitive/behavioral problems was reported in the UK study probably because they performed a cognitive and behavior functioning assessment with a psychometric test while the study in developing countries relied on observation of behavior change. Despite the high level of sleep disturbance observed in this study, no discontinuation of AED was instituted; however some AEDs were modified to reduce the daytime sleep disturbance. The sleep disturbances resolved after 4-8 weeks of treatment probably due to development of tolerance by the patient. This tolerance can be from pharmacokinetic stimulation of hepatic microsomal enzyme induction or from pharmacodynamic alteration in the functioning of receptors [26].

Other CNS ADRs observed include dizziness, fatigue, behavioral problems, headache and blurring of vision. We didn't observe any case of ataxia in contrast to other studies [21,22]. This could be because we didn't use PHT which has been implicated as the cause of ataxia in children on AEDs [21,22].

The second commonest ADR we observed was skin rash; this is similar to previous reports [21,25]. However we didn't observe any case of severe forms of skin rash like erytherma multiforme or Steven-Johnson syndrome. All the skin rashes were mild to moderate, no treatment adjustment was done and they resolved within 1-4 weeks.

Other common ADRs observed include nausea, abdominal pain, increased appetite, and elevated alanine transaminase (ALT). The elevated ALT levels were all less than 2 times the upper limit of normal and didn't necessitate discontinuing or interrupting AED therapy. The ALT all returned to normal levels after 8-12 weeks. The ADRs on the digestive system can be minimized by taking the drugs after food. Increased appetite was primarily due to VPA, 3 of them actually gained weight. Dietary modification and regular exercise should be encouraged in children on VPA to prevent them from developing obesity.

It is important to point out that we observed one patient on VPA that developed gum hypertrophy. PHT and rarely PBT were implicated in all the previous reports of gum hypertrophy in children on AED. The reason for this is not clear and further investigation is needed.

The only reason for discontinuation of an AED was behavioral problem characterised by

excessive hyperactivity in 2 male patients which we attributed to PBT. The 2 patients were on VPA for complex partial seizures and developed hyperactivity few weeks after PBT was added. PBT was substituted with LEV and the hyperactivity resolved gradually over time.

We did not find a significant relationship between ADRs and the age or sex of the patients. However those on polytherapy were significantly more likely to develop ADRs compared to those on monotherapy. This is similar to previous reports [20,21,24]. The goal of AED therapy is to achieve full seizure control with one drug at the lowest possible dose. Monotherapy for epilepsy became standard management in the 1970s as it was recognised that polytherapy was more likely to be associated with drug toxicity [27]. Studies have shown that AED used as monotherapy is effective in 60–70% of children [28-30]. Additional drugs in refractory patients have been shown to be only marginally beneficial [31,32]. However in our community where many of the seizures are not responsive to a single AED, polytherapy will still be used. But we need to reinforce surveillance on our drug procurement system to ensure that only viable and efficacious drugs are dispensed to patients. We also need to create more public awareness on the etiology, treatment and long term outcome of epilepsy in order to reduce the myths and stigma associated with the disease. Additionally we need to change our protocol to the use of lamotrigine as the drug of choice in the treatment of partial seizures in view of the findings of the SANAD study.

4. CONCLUSION

ADRs were common in children on AEDs. The commonest ADRs observed in this study were sleep disturbance, skin rash and dizziness. Children on polytherapy were significantly more likely to develop ADR compared to those on monotherapy. Pharmacovigilance is very important in children on AED so that ADRs can be identified early and managed appropriately, thereby reducing the morbidity and mortality associated with ADRs.

5. LIMITATION

This study has some limitations. Firstly because of the high rate of polytherapy attributing an ADR to a particular drug may be circumstantial. Secondly monitoring the serum drug levels of AEDs is very important when toxicities occur, however, we lack such facilities.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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