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Utilisation of Antiepileptic Drugs in a Tertiary Referral Centre, Southern Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author EUI designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors EPO and EBC managed the analyses of the study. Authors EPO and EBC managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Antiepileptic drug therapy is the mainstay of treatment for the majority of patients with epilepsy. Drug utilisation research is an important aspect of pharmacoepidemiology. It highlights the gaps in the present prescribing practice and helps in improving patient care. This study was aimed at determining the recent prescription pattern of antiepileptic drugs in an ambulatory care setting in Nigeria.
Methods: A cross sectional antiepileptic drug use study was conducted using case notes of epileptic patients managed at the medical outpatient clinic of the University of Uyo teaching hospital, a tertiary referral centre in southern Nigeria between January to December 2017.
Results: Sodium valproate was the most frequently prescribed antiepileptic drug accounting for 46.32% of the prescriptions, followed by carbamazepine and levetiracetam which accounted for 28.42% and 9.47% of the antiepileptic drugs used respectively. Antiepileptic drug combinations were used in 14.46% of the cases studied. Adverse drug reactions were documented in only 3.61% of the cases, while clinically significant drug-drug interaction was noted in 26.51% of the cases.

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Conclusion: Sodium valproate and carbamazepine were the most frequently prescribed antiepileptic drugs in the University of Uyo teaching hospital. Antiepileptic drugs were prescribed mostly as monotherapy. The extent of documentation of adverse drug reactions associated with the use of antiepileptic drugs is poor.

Keywords: Antiepileptic drugs; prescription pattern; pharmacoepidemiology.

1. INTRODUCTION

In the treatment of epilepsy, Antiepileptic drug therapy is the mainstay of management for the majority of patients. Non-pharmacological measures are usually reserved for drug-resistant epilepsy [1].

Several antiepileptic drugs exist, these include the older agents generally regarded as old or established antiepileptic drugs (e.g. Carbamazepine, Phenytoin, Phenobarbitone, Valproic acid etc.) and the newer antiepileptic drugs (e.g. Vigabatrin, Lamotrigine, Felbamate, Gabapentin, Topiramate etc.).The selection of an antiepileptic drug should be based on its efficacy against specific seizure types and the adverse effect profile [2]. Antiepileptic drugs differ in many important aspects including their efficacy against different seizure types, their side-effect profiles, their potential for pharmacokinetic interactions, and their ease of use [3].

A prescription-based survey is considered to be one of the most effective methods to assess and evaluate drug utilisation [4]. Patient case notes and computer registers are widely used as instruments for collecting information on drug utilisation. It is important to consider the recommendations of international bodies on epilepsy, which help to improve prescribing practice and ultimately, clinical standards. A continuous assessment or review is therefore required through systematic audit, which provides feedback from the physician and helps to promote rational use of drugs. Studies on the process of drug utilisation focus on factors related to prescribing, dispensing, administration, and taking of medication, as well as its associated events [5,6].

Changes over time in terms of recommended guidelines often result in modification of the prescription patterns of antiepileptic drugs. Therefore, drug utilisation studies, which evaluate, and analyse the medical, social, and economic outcomes of drug therapy are important as it observes the prescribing attitude of physicians with the aim of ensuring rational drug use. This kind of medical audit highlights the gaps in the present prescribing practice and helps in improving the outcome of patient care [5]. This study was aimed at determining the recent prescription pattern of antiepileptic drugs in an ambulatory care setting in Nigeria.

2. METHODS

A cross sectional antiepileptic drug use study was conducted using case notes of epileptic patients managed at the medical outpatient clinic of the University of Uyo teaching hospital, a tertiary referral centre in southern Nigeria between January to December 2017.

Case notes of patients managed for epilepsy during the period of the study were retrieved and data extracted using data collection instruments. Data collected from the patients' case notes included their age, gender, duration of illness, co-existing diseases, antiepileptic drugs prescribed, the doses and dosing interval of antiepileptic drugs prescribed, documented adverse drug reactions to antiepileptic drugs, the outcome of treatment and documented frequency of therapeutic drug monitoring for antiepileptic drugs requiring drug level monitoring.

Secondary data extracted from the patients' case notes were the appropriateness of the antiepileptic drug doses and dosing interval, drug-drug interactions with antiepileptic drugs, and contraindications to the use of antiepileptic drugs.

The appropriateness of the antiepileptic drug doses, dosing interval and potentially harmful drug interactions were assessed using the British National Formulary - September, 2017 edition [7].

The criterion used in this study to select potentially harmful drug-drug interactions were as follows;

i. Interactions that could potentially cause harmful effects to the patient.
ii. Interactions that could potentially decrease the efficacy of the antiepileptic drugs used.

iii. Interactions that could potentially increase the risk of adverse effects of the drugs used.

Data collected was analysed using Statistical Program for the Social Sciences (SPSS) version 17.0 computer package with descriptive statistics.

3. RESULTS

The clinico-demographic characteristics of the patients and the pattern of utilisation of antiepileptic drugs are presented in Tables 1 and 2 respectively.

As shown in Table 2, there were clinically significant drug-drug interactions in 22 (26.1%) of the cases studied. The drug-drug interactions identified amongst the antiepileptic drugs used were; Carbamazepine + haloperidol 4 (18.18%), Carbamazepine + Diuretics 3 (13.64%), Carbamazepine + Efavirenz 2 (9.09%), Carbamazepine + Isoniazid 1 (4.55%), Carbamazepine + Valproate 1 (4.55%), Valproate + Aspirin [1 (4.55%), Phenytoin + Naproxen 1 (4.55%), Phenytoin + Valproate 1 (4.55%), Carbamazepine + herbal drug 1 (4.55%), Valproate + Amitryptilline 1 (4.55%), Valproate + Clonazepam 1 (4.55%), Valproate + diazepam 1 (4.55%), Carbamazepine + diuretics + fluconazole + antipsychotics 1 (4.55%), Levetiracetam + risperidone + herbal drug 1 (4.55%), Valproate + Herbal drug 1 (4.55%), and Levetiracetam + herbal drug 1 (4.55%).

The doses of antiepileptic drugs prescribed were appropriate in all the cases studied. No contraindication to the use of any antiepileptic drug was noted in all the cases studied.

Table 1. Socio-demographic/clinical characteristics of patients

Parameter	Frequency	Proportion
Gender		
Male	50	60.24
Female	33	39.76
Age group		
16-24	26	31.33
25-34	25	30.12
35-44	11	13.25
45-54	10	12.05
>=55	11	13.25
Seizure type		
Generalised tonic clonic	69	83.13
Simple partial	6	7.23
Complex partial	5	7.23
Diverse seizures	2	2.41
Absence seizures	1	1.20
Duration of Epilepsy (Years)		
<1-5	42	50.60
5-10	13	15.66
11-15	16	19.28
16-20	9	10.84
>20	3	3.61
Co-morbidities		
None	60	72.29
Hypertension	13	15.66
HIV	1	1.21
Peptic ulcer disease	2	2.41
Tuberculosis	1	1.21
Hypertension & Diabetes mellitus	2	2.41
Hypertension & Leukaemia	1	1.21
Hypertension & Asthma	1	1.21
Hypertension & Benign Prostatic Hyperplasia	1	1.21
Hepatitis & Tuberculosis	1	1.21

Table 2. Antiepileptic drug use pattern

Antiepileptic drug prescribed		
Drugs	**Frequency**	**Proportion (%)**
Sodium Valproate	44	46.32
Levetiracetam	9	9.47
Carbamazepine	27	28.42
Phenytoin	6	6.32
Gabapentin	4	4.21
Pregabalin	2	2.11
Clonazepam	1	1.05
Nitrazepam	2	2.11
Antiepileptic drug combinations prescribed		
Monotherapy	71	85.54
Combination therapy	12	14.46
Treatment outcome		
No reduction in seizure frequency	31	37.35
Reduction/Control of seizures	52	62.65
Documented adverse drug reactions		
Yes	3	3.61
None	80	96.39
Drug-Drug interactions		
Present	22	26.51
None	61	73.49
Therapeutic drug monitoring		
Yes	0	0
No	83	100

4. DISCUSSION

We found sodium valproate to be the most commonly prescribed antiepileptic drug. About forty seven percent of the epileptic patients were prescribed sodium valproate (either as a monotherapy or in combination with other antiepileptic drugs) followed by Carbamazepine with about twenty eight percent of the prescriptions. This finding is at variance with the report of a similar study in Ethiopia by Gursha, Agalu and Chanie, where phenobarbitone was the most commonly used antiepileptic drug followed by phenytoin with valproate being prescribed in less than three percent of the cases [8]. However, an Indian study reported valproate as the most commonly used antiepileptic drug, followed by phenytoin and carbamazepine, while a similar report from Jos – Nigeria showed that the most frequently prescribed antiepileptic drugs were carbamazepine and valproate or a combination of the two [9,10]. Variations in the usage of antiepileptic drugs among hospitals and healthcare settings may be as a result of a difference in the clinical presentation of the patients in the different hospitals. Furthermore, a difference in the clinical judgement, training, skill and experience of the attending physicians in the different hospitals as well as the influence of medical detailing from representatives of pharmaceutical companies may also account for these variations.Treatment with anti-epileptic drugs should be selected based on several important considerations including age, co-morbidity, gender, type of seizure or epilepsy, potential adverse effects and potential drug interactions [11]. Epilepsy treatment is generally long-term, hence drug tolerability should be considered as being significantly important for the successful treatment of the condition as it affects compliance to therapy. Valproate is generally well tolerated when given at recommended doses. It is a broad spectrum antiepileptic drug and is used to treat either generalised or focal seizures [12]. This may be a justification for the high utilisation of valproate as observed in our study.

In about eighty five percent of the cases studied, antiepileptic drugs were prescribed as monotherapy. An antiepileptic drug utilisation study in India showed that only nineteen percent of the cases were prescribed antiepileptic drugs as monotherapy, with fifty five percent of the cases placed on dual therapy while twenty six percent of the cases were managed with triple therapy [10]. In Jos - Nigeria, antiepileptic drugs were used as monotherapy in fifty four percent of

the cases and as polytherapy in forty six percent of the cases [13]. Polytherapy in epilepsy management has been reported to offer no advantage over monotherapy. Rather it is considered to increase the potential for drug-drug interactions, to result in a failure to evaluate the individual drugs, to increase the risk of chronic toxicity (including neurocognitive problems), to affect compliance and is also associated with a higher cost of medication and the necessity for therapeutic drug monitoring [14]. On the other hand, the use of monotherapy is associated with better compliance, less side effects and the absence of drug-drug interactions among antiepileptic drugs [8].

In this study, generalised tonic clonic seizure was the most common type of seizure accounting for about eighty three percent of the cases studied. Our finding is in agreement to that obtained from a study in Ethiopia where eighty percent of the cases studied had generalised tonic clonic seizures [8]. However, our result is different from that obtained from a study on the utilisation pattern of antiepileptic drugs at a multispecialty tertiary care teaching hospital in India in which generalised tonic clonic seizures accounted for fifty five percent of the cases [14]. In another study in India, tonic clonic seizure was found in about fifty percent of the study population [10]. Proper classification of seizures and epilepsy type or epileptic syndromes is essential for selecting the most appropriate antiepileptic medication. Lack of proper classification of seizure type affects treatment outcome and selection of drugs.

Antiepileptic drug associated adverse effect was documented in less than four percent of the cases studied with central nervous system side effects being the only adverse effect documented. Although this finding is similar to that reported earlier in India [15], it may not be reflective of the true occurrence of adverse reactions in these patients as poor institutionalised adverse drug reaction reporting system limits proper documentation of adverse reactions in health care settings. A similar study in Ethiopia showed that adverse reactions to antiepileptic drugs was documented in about thirty three percent of the patient medical records reviewed [8]. The prevalence of adverse reactions to antiepileptic drugs in a previous study in Jos – Nigeria was reported to be about twenty eight percent [9]. Antiepileptic drugs can cause various adverse effects and this is an important factor to consider when selecting therapy. Adverse effects of antiepileptic drugs are common and are a major cause of therapeutic failure. Although most of these effects are mild, some adverse effects of antiepileptic drugs may be life-threatening. Many adverse effects of antiepileptic drugs are predictable and usually dose-related [3]. These include rash, blood dycrasias, hyponatraemia (associated with carbamazepine), acute psychotic response and cognitive defects (usually associated with long term use). In patients commencing antiepileptic drug therapy the most common side effects reported are sedation and dizziness. This however, usually resolves with time [3]. Although most antiepileptic drugs can cause common central nervous system side effects, some antiepileptic drugs are more tolerable compared to others [11].

Seizure was either controlled or substantially reduced in about sixty-three percent of the cases studied. Thus, indicating a good response to antiepileptic drug therapy. Regarding epilepsy treatment outcome in terms of seizure freedom, Gursha, Agalu and Chanie in their study showed that almost fifty-seven percent of patients were found to be seizure free for a consecutive 3 year follow-up period. Their study also showed that conventional antiepileptic drugs were still safe and effective for seizure control among a substantial segment of epileptic patients in the resource-poor setting reviewed [8]. Another study carried out in Cleveland – USA reported that sixty-four percent of the cases were completely seizure free in 12 months [16]. Antiepileptic drugs may be withdrawn after at least two years of seizure freedom. Tapering of dose should be done to avoid relapse, increase in frequency and severity of seizures. Seizure relapse is seen in about twenty to forty percent of patients. The age on onset of epilepsy appears to be a significant predictor [11]. In about thirty-seven percent of the cases we studied, there was no significant reduction in seizure frequency. This may be cases of drug resistant epilepsy, a term that has been used to define failure to achieve and sustain seizure freedom in an epileptic patient after the use of two tolerated and appropriate antiepileptic drugs, whether as monotherapies or in combination [17]. Most cases of newly-diagnosed epilepsy respond well to antiepileptic drugs. Poor response to antiepileptic drugs may be due to an inaccurate diagnosis of epilepsy, a wrong choice of drug for the epilepsy syndrome, failure to take the prescribed medication, an underlying cerebral neoplasm, metabolic condition or immune process, concurrent drug or

alcohol misuse [3]. The poor response to antiepileptic drugs as identified in thirty-seven percent of the cases in this study may be due to the patients' poor adherence to antiepileptic therapy. Medication non-adherence usually results in poor clinical outcomes, increase in morbidity and mortality, and an increase in healthcare expenditure. Reports indicate that about 50%–60% of patients are non-adherent to the medicine prescribed by their physician, particularly patients with chronic diseases [18]. Non-adherence to antiepileptic medications has been reported to be high. Studies have shown a high prevalence of seizure (21–45%) in patients who did not adhere to their antiepileptic medications [13]. More than half of epileptic patients have poor seizure control due to non-adherence to medications [19]. More than 30% of people with epilepsy do not attain full seizure control even with the best available treatment regimen. Failure to have a controlled seizure in such significant proportion of epileptic patients is attributed to poor adherence to medications [20]. The patients' beliefs about cause of epilepsy and preference to the treatment modality are important factors influencing epilepsy treatment. Patients' own attitudes towards the treatment are also equally important in ensuring success of treatment and adherence [21]. Failure to adhere through forgetfulness, misunderstanding, or uncertainty about clinician's recommendations, or intentionally due to their own expectations of treatment, side-effects, and lifestyle choice are found to be the reasons for non-adherence [22].

Clinically significant potential drug-drug interactions were found in about 27% of the cases. The potential interactions noted were carbamazepine-haloperidol interaction, carbamazepine-diuretic interaction, valproate-amitryptilline, amongst others. Carbamazepine accelerates the metabolism of haloperidol causing a reduced plasma concentration of haloperidol. Carbamazepine, when used alongside diuretics, increases the risk of hyponatremia [7].

Generally, the anticonvulsant effects of antiepileptic drugs are antagonised by antidepressants including the selective serotonin re-uptake inhibitors and the tricyclic antidepressants. The use of carbamazepine and valproate as combination therapy results in a reduction in the plasma concentration of valproate, while increasing the plasma concentration of the active metabolites of carbamazepine. There is an increased risk of side effects when valproate is used concomitantly with clonazepam. Furthermore, the effect of valproate is enhanced by aspirin, while the plasma concentrations of diazepam and lorazepam are increased by valproate [7].

The potential for clinically significant drug-drug interaction should be of paramount consideration during the selection of the type and doses of antiepileptic drugs, particularly when they are used in combination (combination therapy) or when they are used with other non-antiepileptic medications in patients with co-morbidities.

Therapeutic drug monitoring was not carried out in any of the cases studied. The measurement and interpretation of serum concentrations of antiepileptic drugs can be of profound benefit in the treatment of uncontrollable seizures. Therapeutic drug monitoring enables more decisive and effective optimisation of therapy and disease management [23]. The lack of therapeutic drug monitoring as revealed in this study may be due to the pervasive problem of non-availability of the required facilities to carry out such investigations, a problem that appears to be common in resource poor settings.

The doses and dosing of antiepileptic drugs prescribed as documented in the patient case notes were appropriate in all the cases studied. No contraindication to the use of any antiepileptic drug was noted. This is commendable but expected as the study was carried out in a tertiary health facility with specialised services.

5. CONCLUSION

Sodium valproate and carbamazepine were the most frequently prescribed antiepileptic drugs in the University of Uyo teaching hospital. Antiepileptic drugs were prescribed mostly as monotherapy. The extent of documentation of adverse drug reactions associated with the use of antiepileptic drugs in this hospital is poor. There was no reduction in seizure frequency in a significant proportion of patients placed on antiepileptic drugs. There were clinically important potential drug-drug interactions in a significant proportion of the antiepileptic drug prescriptions studied.

CONSENT

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

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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