Pattern of utilization of antiepileptic drugs in the first 12 months of epilepsy treatment in children

Emeka U Ejeliogu[1,2], Aderonke Courage[2], Mary Bok[2], Esther S Yiltok[1,2]

Abstract

Background: Drug utilization studies are important methods of assessing how drugs are used in the society. Without the knowledge of how drugs are being prescribed and used, it is difficult to initiate discussion on rationale drug use and to suggest measures to change prescribing habits for better management of patients. This study therefore aimed to evaluate the pattern of utilization of antiepileptic drugs (AEDs) in the first 12 months of epilepsy treatment in children in Jos, Nigeria.

Methods: A case record form was used to document all relevant information of children with epilepsy that were commenced on AED from January 2011 to December 2015. Information collected in the first 12 months of commencement of AED was used to evaluate the pattern of utilization of AEDs among the study subjects. Information obtained was analyzed with statistical package for social sciences software version 20.

Results: Three hundred and eighty one subjects with a median age of 5.4 years were studied. The most frequently prescribed drug at commencement of epilepsy treatment was Carbamazepine (CBZ) (75.9%) followed by Sodium Valproate (VPA) (17.1%) while the most frequent AED combination was CBZ+VPA. Despite the fact that all the patients were commenced on monotherapy, the rate of polytherapy at 12 months was 35.2%. Deviation from standard treatment guidelines was observed in 127 (33.3%) of the subjects with the most common deviation being the use of CBZ for generalized tonic-clonic seizures.

Conclusion: Significant deviations were observed in the utilization of AEDs in children with epilepsy. Using standard guidelines in the treatment of childhood epilepsy will reduce the rate of uncontrolled seizures and improve their long term outcome.

Keywords: Epilepsy, Children, Antiepileptic drugs, Pattern, Utilization

Highland Med Res J 2020;20(1):30-34

Introduction

Epilepsy is a chronic brain disorder characterized by recurrent seizures that affects approximately 50 million people worldwide, of which >80% reside in developing countries.[1-3] Its overall annual incidence ranges from 50–70 cases per 100,000 in industrialized countries and up to 190 per 100,000 in developing countries.[3] In Nigeria, it is the commonest neurologic disorder affecting children and this has been attributed to the high incidence of intracranial infection and adverse perinatal events such as asphyxia and severe neonatal jaundice.[4]

The goal of treatment of epilepsy includes minimizing the risk of recurrent seizures and antiepileptic drug (AED) side effects, and maintaining normal psychosocial and educational/vocational adjustment.[5] AEDs are either used singly or in combinations. The choice of AED to be used for individual patients depends on a number of factors including the seizure type or epileptic syndrome present, the efficacy of the drug, its side effects, patient's characteristics including the presence of comorbidities and their treatability by the same AED, availability, cost and convenience of dosing.[5] These factors may have produced some variations in the use of AEDs. Different epilepsy types may be particularly responsive to specific AEDs but some AEDs have multiple mechanism of action with a broad spectrum of activity across a range of seizure types.

If a decision is made to initiate AED therapy, it is better to start with monotherapy, as more than 60% of all patients can be treated with one drug and considered well controlled, even if they may not become necessarily seizure free.[6,7] But, if monotherapy is not found satisfactory, it is possible to combine AEDs having different mechanisms of action.[6,7]

Without the knowledge of how drugs are being prescribed and used, it is difficult to initiate discussion on rationale drug use and to suggest measures to change prescribing habits for better management of patients.[8,9] Drug utilization studies are important exploratory methods of assessing how drugs are used in the society. They create a sound socio-medical and health economic basis for health care decision making. Drug utilization studies play a pivotal role in directing towards rational drug prescribing, thus minimizing the possibilities of adverse effects and helping improvement of patient

[1]Department of Paediatrics, University of Jos, Nigeria.
[2]Department of Paediatrics, Jos University Teaching Hospital, Jos, Nigeria.

All correspondences to:
Dr. Emeka U. Ejeliogu
Email: emekam12@yahoo.com

compliance and resultant quality of life.[10]

There is no standard guideline for treatment of childhood epilepsy in Nigeria. The World Health Organization (WHO) guidelines recommend the use of Phenobarbitone as first-line AED for treatment of childhood epilepsy in non-specialized health settings because of its low acquisition cost.[11] Previous studies from other parts of the country reported that Carbamazepine (CBZ) was the most commonly used AED followed by Sodium Valproate (VPA) and Phenobarbitone.[12,13] There is no published data on AED utilization among children in Jos, Nigeria. This study was therefore aimed to evaluate the pattern of utilization of AEDs among children with epilepsy at Jos University Teaching Hospital, Jos, Plateau State, Nigeria

Patients and Methods

Study Site

This study was carried out in the pediatric neurology clinic of Jos University Teaching Hospital, Jos, Nigeria. The clinic runs every week at the pediatric out-patient department (POPD) of the hospital. It attends to about 40 patients every clinic day. About 50% of children attending the clinic have epilepsy.

Study Population

Subjects of the study were children less than 18 years of age with newly diagnosed epilepsy that were commenced on antiepileptic drug (AED) from January 2011 to December 2015 and had received AED for at least 12 months.

Study Design

This was a retrospective study.

Data Collection

A case record form was used to document all relevant information of each patient at 12 months after commencement of AED. Information collected included socio-demographic data, type of epilepsy, date of commencement of AED, type of AED, dose of AED, change of AED therapy, reason for changing AED, number of AEDs, and duration of AED therapy.

Data Analysis

Data obtained was analyzed with statistical package for social sciences (SPSS) software version 20. Results were presented in descriptive statistics using frequency tables.

Ethical Consideration

Ethical approval for the study was obtained from the Human Research and Ethics Committee of Jos University Teaching Hospital.

Results

Three hundred and eighty one subjects met the inclusion criteria and were recruited for the study. Males were 225 (59.1%) while females were 156 (40.9%). The median age of the patients at onset of seizure was 4.8 years (interquartile range (IQR) 2.2-7.4 years)while the median age at presentation was 5.4 years (IQR 2.9-8.6 years). Table 1 shows the characteristics of the patients.

Table 1. Characteristics of the patients

Characteristics	n	%
Sex		
Males	225	59.1
Females	156	40.9
Age group		
<1year	43	11.3
1-5years	167	43.8
6-10years	145	38.1
11-17years	26	6.8
Type of Seizure		
Generalized	277	72.7
Tonic-clonic	182	65.7
Myoclonic	9	3.2
Atonic	23	8.3
Absence	27	9.8
Epileptic spasms	5	1.8
Mixed	31	11.2
Focal	104	27.3
Aware	15	14.4
Awareness impaired	89	85.6
Etiology of seizure		
Genetic	47	12.3
Structural	78	20.5
Metabolic	5	1.3
Infectious	81	21.3
Unknown	170	44.6
Antiepileptic Regimen at 12 months		
Monotherapy	247	64.8
Polytherapy	134	35.2

All the patients were initially commenced on monotherapy. Twelve months after commencement of AED, two hundred and forty seven (64.8%) were on monotherapy, 116 (30.5%) were on two AEDs while 18 (4.7%) were on three AEDs. The most frequently prescribed drug at commencement was Carbamazepine (75.9%), however at 12 months the frequency of its use as monotherapy had reduced to 38.6%. Table 2 shows the frequency of use of AEDs at commencement and at 12 months.

Table 2. AED Regimen at commencement and at 12 months

Regimen	At commencement		At 12 months	
	N	%	n	%
Carbamazepine	289	75.9	147	38.6
Sodium Valproate	65	17.1	81	21.3
Ethosuximide	25	6.6	19	4.9
Prednisolone	2	0.5	0	0
CBZ+VPA	-	-	108	28.4
CBZ+LEV	-	-	5	1.3
VPA+LEV	-	-	3	0.8
CBZ+VPA+PBT	-	-	13	3.4
CBZ+VPA+LEV	-	-	5	1.3

CBZ, carbamazepine; VPA, Sodium valproate; PBT, phenobarbitone; LEV, levetiracetam

Table 3. Deviations in use of AEDs in relation to standard guideline

Type of seizure	Recommended first-line AED	No of deviations	% of deviation
Generalized tonic-clonic	Sodium Valproate	121	66.5
Myoclonic	Sodium Valproate	1	11.1
Atonic	Sodium Valproate	2	8.7
Absence	Ethosuximide/Sodium Valproate	0	0
Epileptic spasms	ACTH/Prednisolone/ Vigabatrin	3	60
Focal seizures	Carbamazepine/ Lamotrigine	0	0

AED, Antiepileptic drug; ACTH, Adrenocorticotrophic hormone

Table 3 shows the frequency of deviation in use of AEDs in relation to standard guidelines. Deviations were observed in 127 (33.3%) of the subjects, the most frequent deviation was using CBZ for generalized tonic-clonic (GTC) seizures.

Discussion

This study was carried out to evaluate the utilization of AEDs among children with epilepsy at Jos University Teaching Hospital. There is no national guideline for the management of childhood epilepsy in Nigeria. The World Health Organization (WHO) guidelines recommend the use of Carbamazepine (CBZ), Sodium Valproate (VPA), Phenytoin and Phenobarbitone for treatment of childhood epilepsy in non-specialized health settings.[11] This guideline also recommends the use of Phenobarbitone as first-line AED for treatment of childhood epilepsy because of its low acquisition cost, and CBZ for focal seizures if available.[11]Phenobarbitone can cause cognitive dysfunction in children,[14,15] as such most paediatricians at specialized health settings such as teaching hospitals do not use it for long term treatment of seizures in children. Phenytoin has narrow therapeutic index and dose-dependent pharmacokinetics, dosage adjustments is usually guided by serum drug level monitoring.[16,17] Because of the unavailability of serum drug level monitoring, it is not commonly used in Nigeria. Considering that our hospital is a specialized teaching hospital, we use standard guidelines based on international best practices for management of childhood epilepsy at the clinic. We also consider local circumstances especially cost and availability of drugs. The National Clinical Guideline Centre of United Kingdom[18] and The subcommittee of the American Academy of Neurology and the American Epilepsy Society[19] both recommend the use of CBZ or Lamotrigine (LTG) for treatment of focal seizures, and VPA for generalized and unclassifiable seizures.

Based on standard guidelines, all our patients were commenced on monotherapy. The most frequently prescribed AED was CBZ followed by VPA. Considering that most of the patients had generalized seizures, many of the patients with generalized seizures were commenced on CBZ instead of VPA. Despite the fact that CBZ has broad spectrum activity on seizure control, VPA is the most effective AED in generalized seizures.[18-20] Though CBZ is recommended as an alternative AED in GTC seizures, it can worsen other types of generalized seizures like myoclonic, tonic/atonic, and absence seizures. Also because of the mechanism of action, it is contraindicated in seizures that are associated with abnormalities in the voltage-gated sodium channels like Dravet syndrome.[21] Using CBZ for generalized seizure will reduce the number of children that will achieve the all-important goal of seizure control. The rate of utilization of CBZ is similar to 71% reported in Abuja, Nigeria[13], but lower than the 40.4% reported in Ibadan, Nigeria.[12] Sykes reported that Phenobarbitone was the most commonly used AED in Benin, Nigeria,[22] the study was however done 18 years ago.

Despite the fact that all the patients were commenced on monotherapy, the rate of polytherapy at 12 months was 35.2%. The rate of polytherapy in our study was higher than what was reported in UK[23] and India.[24] Many factors could have contributed to the higher rate of polytherapy in this study. Firstly we used CBZ for a large proportion of patients with generalized seizure which may not have controlled the seizures therefore necessitating adjunctive therapy. Secondly it could 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.[25-27] 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 recognized that polytherapy was more likely to be associated with drug toxicity.[28] Studies have shown that AED used as monotherapy is effective in 60–70% of children.[29-31] Additional drugs in refractory patients have been shown to be only marginally beneficial.[32,33]

The deviation rate of 33.3% in the utilization of AEDs in this study was lower than the 53.3% reported in India.[34] The most common deviation observed in this study was the use of CBZ instead of VPA for GTC seizures, this accounted for 124 (97.6%) of the 127 deviations. In contrast, the study in India reported that the most common deviation was the use of VPA for focal seizures. Because VPA is more effective than CBZ in generalized and unclassifiable seizure,[18,19] every effort should be made to use it as first-line AED in children with generalized seizures.

We also observed some deviations in the treatment of epileptic spasms. The standard recommended AEDs for epileptic spasms are Adrenocorticotrophic hormone (ACTH) or Prednisolone for those without tuberous sclerosis, and Vigabatrin for those with tuberous sclerosis.[18] Vigabatrin can cause irreversible peripheral visual field defects in children[35,36] Age-appropriate visual field testing is recommended at baseline and then repeated at intervals in patients who continue therapy, but it is difficult to perform in children less than 9 years.[37] Vigabatrin was also not available at our center and could not be procured in the country.

Despite the fact that all the patients were commenced on recommended dosage of each AED, we observed other deviations in respect to drug therapy. Not all the patients had their AED dosage increased every 2 weeks if seizures were not controlled. Some were on same dosage of AEDs for some months even though they were still having seizures. Some were given long appointments before seizures were controlled because they came from far distances. Another deviation observed was that a second AED was added without reaching the maximum dosage of the first AED. This also contributed to the high rate of polytherapy observed in the study.

This study has some limitations. Firstly it was a retrospective study and it could have affected the quality of data collected. Secondly the sample size was relatively small; there is need to conduct larger prospective studies. However, it is hoped that the findings of this study will help to improve the quality of care of children with epilepsy at the pediatric neurology clinic of the hospital will lead to better long term outcomes. It will also assist other clinicians managing children with epilepsy in providing good quality care.

In conclusion, the commonest AED used for treatment of epilepsy in children at Jos University Teaching Hospital was CBZ followed by VPA. We observed significant deviations in the use of AEDs in relation to standard guidelines. The major deviation was the use of CBZ instead of VPA for treatment of generalized tonic-clonic seizures. Using standard guidelines in the treatment of childhood epilepsy will reduce the rate of uncontrolled seizures and improve their long term outcome.

References

1. Leppik IE. Contemporary diagnosis and management of the patient with epilepsy. 5th ed. Newtown, PA: Handbooks in Healthcare Company; 2001:155-156.
2. World Health Organization. Atlas of Epilepsy Care in the World. Geneva WHO 2005. Available at https://www.who.int/mental_health/publications/atlas_epilepsy_care_2005. Accessed on 13/12/2019.
3. Wahab A. Difficulties in treatment and management of epilepsy and challenges in new drug development. Pharmaceuticals. 2010;3:2090-2110.
4. Ogunlesi T, Ogundeyi M, Olowu A. Pattern of childhood epilepsies in Sagumu, Nigeria. Indian J Pediatr. 2009;76:385-389.
5. Fountain NB. Choosing among antiepileptic drugs. Continuum (MinneapMinn). 2010;16(3 Epilepsy):121-135. doi:10.1212/01.CON.0000368235.64857.cf
6. Brodie MJ, French JA. Management of epilepsy in adolescents and adults. Lancet.2000;356:323-329.
7. Mattson RH. Antiepileptic drug monotherapy in adults: selection and use in new-onset epilepsy. In: Levy RH, Mattson RH, Meldrum BS, eds. Antiepileptic drugs. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:72-95.
8. Phillips MS, Gayman JE, Todd MW. ASHP guidelines on medication-use evaluation. American Society of Health-system Pharmacists. Am J Health Syst Pharm. 1996;53(16):1953-1955. doi:10.1093/ajhp/53.16.1953.
9. World Health Organization. Drug and therapeutics committees: a practical guide. Holloway K (editor), Green T. World Health Organization 2003. Available at https://apps.who.int/iris/handle/10665/68553. Accessed on 20/01/2020.
10. Fatima E, Anwar A, Dudeja M, et al. Drug utilization pattern and adverse drug reaction monitoring in urinary tract infection patients in a tertiary care hospital. JDDT [Internet]. 2015;5(6):23-30. Available from: http://jddtonline.info/index.php/jddt/article/view/1103. Accessed on 20/01/2020.
11. World Health Organization. Evidence-based recommendations for management of epilepsy and seizures in non-specialized health settings. Geneva, WHO 2012. Available at https://www.who.int/mental_health/mhgap/evidence/epilepsy/en/. Accessed on 21/01/2020.

12. Lagunju IOA, Fatunde OJ, Takon I. Profile of childhood epilepsy in Nigeria. J Pediatr Neurol. 2009;7:135-140.
13. Shatima DR, Ulonnam CC, Author C. The Pattern of Childhood Epilepsies at National Hospital Abuja Nigeria. Journal of Medical Science and clinical research 2014;2:1367-1377.
14. Thompson PJ, Trimbler MR. Anticonvulsant drugs and cognitive functions. Epilepsia 1982; 23: 531-44.
15. Ogunrin O, Adamolekun B, Ogunniyi A. Cognitive Effects of Anti-Epileptic Drugs in Nigerians with Epilepsy. African Journal of Neurological Sciences. 2005;24:6-11.
16. Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs - best practice guidelines for therapeutic drug monitoring: A position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008;49:1239–1276.
17. Wu MF, Lim WH. Phenytoin: a guide to therapeutic drug monitoring. Proceedings of Singapore Healthcare 2013;22:198-202.
18. National Clinical Guideline Centre (UK). The Epilepsies: The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care. London: Royal College of Physicians (UK); 2012. Available at https://www.ncbi.nlm.nih.gov/books/NBK247130/. Accessed on 21/01/2020.
19. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2004;62:1252-1260.doi:10.1212/01.wnl.0000123693.82339.fc
20. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet. 2007;369:1016-1026.
21. de Lange IM, Gunning B, Sonsma ACM, et al. Influence of contraindicated medication use on cognitive outcome in Dravet syndrome and age at first afebrile seizure as a clinical predictor in SCN1A-related seizure phenotypes. Epilepsia. 2018;59:1154-1165.
22. Sykes RM. Epilepsy in children in Benin City, Nigeria. Ann Trop Paediatr. 2002;22:287–296.
23. Anderson M, Egunsola O, Cherrill J. A prospective study of adverse drug reactions to antiepileptic drugs in children. BMJ Open. 2015;5:e008298.
24. Suman A, Gosavi DD. Study of Adverse Drug Effects of Antiepileptic Drugs used in Pediatric Patients in a Tertiary care rural Hospital–a Pharmacovigilance Study. J Young Pharm. 2017;9:60-64.
25. Klantschnig G, Huang C. Fake drugs: health, wealth and regulation in Nigeria. Review of Africa Political Economy. 2019;46:442-458.
26. Fatokun O. Curbing the circulation of counterfeit medicines in Nigeria. The Lancet. 2016;388:2603-2609.
27. Akiny O. Counterfeit drugs in Nigeria: A threat to public health. African Journal of Pharmacy and Pharmacology. 2013;7:2571-2576.
28. Shorvon S, Chadwick D, Galbraith A. One drug for epilepsy. Br Med J. 1978;1:474-476.
29. Dudley RW, Penney SJ, Buckley DJ. First-drug treatment failures in children newly diagnosed with epilepsy. Pediatr Neurol. 2009;40:71-77.
30. Ma MS, Ding YX, Ying W. Effectiveness of the first antiepileptic drug in the treatment of pediatric epilepsy. Pediatr Neurol. 2009;41:22-26.
31. Carpay HA, Arts WF, Geerts AT. Epilepsy in childhood: an audit of clinical practice. Arch Neurol. 1998;55:668-673.
32. Berg AT, Levy SR, Testa FM. Remission of epilepsy after two drug failures in children: A prospective study. Ann Neurol. 2009;65:510-519.
33. Kanner AM, Balabanov AJ. The use of monotherapy in patients with epilepsy: An appraisal of the new antiepileptic drugs. Curr Neurol Neurosci Rep. 2005;5:322-328.
34. Raphael J, John NN. Drug Utilisation Pattern of Anti-Epileptic Agents among Paediatric Patients with Epilepsy. International Journal of Pharmacy Research and Health Sciences. 2019;7:3043-3046.
35. Nousiainen I, Mantyjarvi M, Kalviainen R. No reversion in vigabatrin-associated visual field defects. Neurology. 2001;57:1916-1917.
36. Spencer E, Harding G. Examining visual field defects in pediatric population exposed to vigabatrin. Doc Ophthalmol. 2003;107:281-287.
37. Willmore LJ, Abelson MB, Ben-Menachem E, et al. Vigabatrin: 2008 update. Epilepsia. 2009;50:163-173.