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ASSESSMENT OF PRESCRIBING PATTERN OF ANTIEPILEPTICS IN PAEDIATRIC IN-PATIENTS OF A TERTIARY CARE HOSPITAL

Juny Sebastian¹, Merina Fracncis Mathew¹, P. Amuktha¹, Aswani Chacko¹ and D. Narayanappa²

Department of Pharmacy Practice - JSS College of Pharmacy¹, Department of Pediatrics - JSS Medical College & Hospital², JSS Academy of Higher Education and Research, SS Nagara, Mysuru - 570015, Karnataka, India.

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Correspondence to Author:

Juny Sebastian

Lecturer,
Department of Pharmacy
Practice, JSS College of Pharmacy,
JSS Academy of Higher Education
and Research, SS Nagara, Mysuru -
570015, Karnataka, India.

E-mail: junysebastian@jssuni.edu.in

ABSTRACT: Purpose: To study the prescribing pattern of AEDs for a different type of seizures in the pediatric population and disease conditions other than epilepsy and to identify the drug interactions with the use of AEDs among the study population. **Methods:** This six months long prospective observational study was conducted at in-patient wards of JSS Hospital. The case sheets of all in-patients were reviewed daily and enrolled the patient's who met the study criteria. Enrolled children were followed until discharge to identify the usage pattern of AEDs and other drug therapy and any drug interactions involved in the use of AEDs. **Results:** Total number of the study population was 294, and the mean age of the study population was 8.64 ± 3.7 years, and the majority of the then were infants [1 month - 1 year (35.03%)], followed by toddlers [1-2 years (32.6%)]. In our study, the majority of children were on monotherapy (64.96%) followed by dual therapy (26.53%). Clobazam was the highly prescribed drug as monotherapy (39.79%), and fosphenytoin + clobazam was majorly used dual therapy (26.92%) combination. A total of 39 treatment charts had AED - AED interactions, but none of those were clinically significant. **Conclusion:** Among the study population, only 64.96% responded to monotherapy while others required combination therapy due to the seizure type and co-morbid conditions. We couldn't identify any drug-related problems among the study population as the AED therapy was more judicious and wherever necessary the pediatricians have taken the advice of neurologists to avoid any errors.

INTRODUCTION: Epilepsy is a chronic neurological disorder affecting people across the globe¹. Over 10 million children worldwide are believed to have epilepsy². According to the World Health Organization (WHO), of the 50 million people with epilepsy worldwide, 80% reside in developing countries.

Worldwide, the prevalence of active epilepsy ranges from 4 to 5 per 1000 population and in India, the prevalence rate of epilepsy ranges between 4.15 and 7.03 per 1000 population³.

Its incidence is highest during childhood, with a median incidence for children aged zero - 14 years of 0.822 per 1000 children. It has also been estimated that 70% of all epilepsy syndromes start between the age of zero and 19 years and 30% of the children with seizures will have their first episode before the age of 4 years, and more than half of the children with epilepsy will have more than one type of seizure⁴.

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The incidence of epilepsy is quite high in the pediatric population, and the epileptic management is also troublesome as they are anatomically and physiologically different from a normal healthy adult in terms of weight and surface area³. The physiological systems are also in a growing phase that contributes to differences in the rate and extent of drug absorption, metabolism, excretion (pharmacokinetics) as well as pharmacodynamic effect as compared to a normal healthy adult. Concomitant diseases and drugs may complicate pharmacotherapy⁵. Another common problem encountered in children is a failure to comply with therapeutic regimen due to either inconvenient dosing schedule and a large number of medicines prescribed⁶. The general approach for epilepsy management involves the identification of goals, assessment, and development of care plan and follow up evaluation. Treatment goals remain same for all patients irrespective of seizure type and age of patients which is the initiation of an appropriate antiepileptic drug (AED) therapy to stop the occurrence or reduce the frequency of seizures with minimal adverse effects, which in turn improve the patient's quality of life⁸. The outcome of AED therapy in children depends on many factors, including selection, dosing, and monitoring of AEDs, the identification of underlying cause, the type of seizures and the pharmacokinetic parameters of AEDs².

During the assessment phase, it is critical to establish an accurate diagnosis of seizure type and exact classification. Most of the times, accurate diagnosis of seizure depends only on eye witness of the seizure attacks. Sometimes seizure occurs at the night, and the patient may not be aware of the seizure attack, which will go unnoticed and unreported. The choice of the most appropriate drug treatment for a patient with seizures depends upon the accurate classification of the seizures, the type of epilepsy or epileptic syndromes, and drugs such as availability and accessibility, efficacy, side effect profile and ease of use as well as patient factors⁷.

Over 80% of epileptic patients can achieve a significant reduction in seizure frequency with one drug alone. But the remaining 20% of patients may require dual therapy for seizure control. In such situations, the patients may have an economic

burden along with drug-related problems such as ADRs, drug interactions, *etc.* These all factors may influence the antiepileptic medication compliance in epileptic patients. Risk of adverse effects and drug interactions are less in pediatrics compared to elderly patients⁷. According to National Institute of Clinical Excellence (NICE) guidelines, it is recommended that children should be treated with monotherapy wherever possible and if initial treatment with a single AED is unsuccessful, then the child should be treated with another single AED. Rational selection of AED in different seizures depends on its efficacy in various types of seizures and other co-morbid medical conditions. While choosing an antiepileptic drug, factors such as the mechanism of action, ease of dosing, long term adverse effects, neuropsychiatric profile, sedative burden and interaction to other drugs, *etc.* should be considered⁹.

OBJECTIVES: To study the prescribing pattern of AEDs for a different type of seizures in the pediatric population and disease conditions other than epilepsy and to identify the drug interactions with the use of AEDs among the study population.

METHODOLOGY: The prospective observational study was carried out for a period of six months from October 2016 to March 2017 at in-patient pediatric Department of JSS Hospital (JSSH), Mysuru, which is a multi-specialty Tertiary Care Teaching Hospital with bed strength of 1800. Pediatric in-patient Department of JSSH consists of 115 bedded ward, 10 bedded pediatric intensive care unit (PICU) and 40 bedded neonatal intensive care unit (NICU). The study enrolled pediatric in-patients receiving at least on AED from the ward and PICU. Those patients' length of hospital stay is less than a day and those who shifted to other clinical departments and hospitals on the day of admission is excluded from the study. The case sheets of all in-patients were reviewed daily and enrolled the patient's who met the study criteria. All the relevant information were collected from their case sheets and by interviewing their caretakers and health care professionals and documented in a suitably designed data collection form. Enrolled children were followed until discharge to identify the usage pattern of AEDs and other drug therapy as well as for drug-drug interaction. The data collected was entered online

into a specially designed 'Google Form' for easy accessibility, retrieval, and analysis of the data.

Ethical Clearance: The local Institutional Human Ethical Committee approved this study.

RESULTS:

General Details of the Study: A total of a number of the study population was 294, of the 66.3% were boys, and 33.6% were girls. The mean age of the study population was 8.64 ± 3.7 years, and the majority of the then were infants [1 month - 1 year (35.03%)], followed by toddlers [1 - 2 years (32.6%)]. Demographic details of the study population are present in **Table 1**.

TABLE 1: DEMOGRAPHIC DETAILS OF THE STUDY POPULATION

Characteristics		No. of patients	Percentage
Gender	Male	195	66.3%
	Female	99	33.3%
Age group	New born (birth- 1 month)	0	0
	Infants (1 month- 1 year)	103	35.03%
	Toddler (1-2 years)	96	32.65%
	Child (2- 12 years)	80	27.21%
	Adolescents (12-18years)	15	5.10%

A total of 36.39% (n=107) had a history of seizure disorder, and among them, 59 children had a history of febrile seizures and 48 children were diagnosed with generalized tonic-clonic seizures (GTCS) and 74.13% of them were on regular AED therapy. Most of the study population (62.36%)

TABLE 2: DUAL THERAPY COMBINATIONS

	Clobazam	Carbamazepine	Sodium valproate	Levetiracetam	Lorazepam	Phenobarbitone
Fosphenytoin	21(26.92%)	3(3.84%)	16(20.51%)	6(7.69%)	6(7.69%)	6(7.69%)
Sodium valproate	8(10.25)	2(2.56%)	-	6(7.69%)	2(2.56%)	-
Lorazepam	2(2.56%)	-	2(2.56%)	-	-	-
Clobazam	-	1(1.28%)	-	-	-	2(2.56%)

Out of the 18 children prescribed with triple therapy, most commonly seen combinations were fosphenytoin + clobazam+ valproate (n=4) followed by fosphenytoin+ levetiracetam+ sodium valproate (n=4), clobazam + valproate + levetiracetam (n=3), fosphenytoin + clobazam + carbamazepine (n=3), fosphenytoin + clobazam + lorazepam (n=2) and fosphenytoin + levetiracetam + phenobarbitone (n=2). Out of the 7 children prescribed with quadruple therapy, commonly seen combination was fosphenytoin + levetiracetam + valproate + clobazam in 4 children followed by

presented with simple febrile seizures, 15.5% with complex febrile Seizures and 12.24% presented with GTCS.

AED Therapy: In our study, the majority of children were on monotherapy (64.96%) followed by dual therapy (26.53%). Clobazam was the highly prescribed drug as monotherapy(39.79%), followed by fosphenytoin /phenytoin (34.55%). Clobazam use was more as it is the indicated drug for the treatment of febrile seizures and fosphenytoin/ phenytoin for GTCS and status epilepticus. And previous studies show that simple febrile seizures were treated with diazepam in the acute stage and therapy was maintained with clobazam. The latter drug is preferred as maintenance therapy to prevent recurrence. It has fewer side effects like ataxia and drowsiness compared to diazepam and also ensures better patient compliance. Sodium valproate (4.71%), phenobarbitone (2.61%) and carbamazepine (2.09%) also used in our study population as monotherapy. The data obtained about dual therapy in 78 children revealed that a combination therapy of fosphenytoin + clobazam was prescribed in a maximum number of children (26.92%), followed by a combination of fosphenytoin + valproate in (20.51%) of children and less commonly seen combination was carbamazepine + valproate. The dual therapy combination found in our study is presented in **Table 2**.

fosphenytoin + levetiracetam + valproate + phenobarbitone in 3 children.

Administration Pattern of AEDs: Most of AEDs were administered through oral route than parenteral because oral administration is easy and painless and most preferred in the paediatric population. One-third of our children (n=100) received AED *via* route and the remaining received AED *via* both oral and parenteral route. The most commonly used oral AED was Clobazam (48.41%), followed by phenytoin irrespective of the

type of therapy. Fosphenytoin was the frequently prescribed AED parenterally (70.1%), followed by sodium valproate (13.4%).

AED Use in Disease Conditions Other than Epilepsy: Out of 108 children treated with AED for disease conditions other than epilepsy, meningitis was the most commonly seen brain infection followed by encephalitis and acute disseminated encephalomyelitis (ADEM). Hypocalcemic seizures were observed in 17 children. The details are presented in **Table 3**.

TABLE 3: AEDs USE AMONG CONDITIONS OTHER THAN EPILEPSY

Disease	No. of patients
Brain infections	
Meningitis	14
Encephalitis	8
ADEM	6
Hypocalcemic seizures	17
Dengue shock syndrome	4
Post-rabies vaccine encephalopathy	2
Diphtheria pertussis and tetanus vaccine-induced encephalopathy	4
Acute poisoning	3

Among the 146 children who had co-morbid conditions, the majority of the children (36.9%) had respiratory tract infections (RTI), followed by dengue fever (10.95%), gastritis (8.9%), and protein-energy malnutrition (7.53%). Few patients had anemia, rickettsial fever, developmental delay, cerebral palsy, spastic triplegia, urinary tract infections (UTI) and mental retardation as co-morbidities. The previous study also revealed that RTI and gastroenteritis remained most commonly associated co-morbid condition and few patients had UTI, migraine, metabolic disorder, skin infection as co-morbidity as shown in our study ². Details are presented in **Table 4**.

TABLE 4: DIFFERENT CO-MORBID CONDITIONS ASSOCIATED WITH SEIZURES

Co-morbid condition	No. of patients	Percentage
Mental retardation	3	2.04%
Developmental delay	4	2.73%
Cerebral palsy	6	4.1%
Spastic triplegia	4	2.73%
Protein-energy malnutrition	11	7.53%
Anemia	9	6.16%
Gastritis	13	8.9%
Rickettsial fever	9	6.16%
Respiratory tract infection	54	36.9%
Urinary tract infection	8	5.47%
Dengue fever	16	10.95%
Others	9	6.16%

Among the drug classes used along with AEDs, most commonly prescribed group of drugs was antibiotics in (82.31%) children followed by analgesics (74.14%), proton pump inhibitors in 169 (57.48%).

Drug-Related Problems among the Study Population: Out of 294 treatment charts reviewed, 39 treatment charts had AED- AED interactions. The most commonly observed AED- AED interaction was carbamazepine + sodium valproate interaction (n=8) followed by carbamazepine + fosphenytoin (n=7). The details are presented in **Fig. 1**. The most commonly seen AED- other class interaction was clobazam+ omeprazole interaction (n=20), followed by fosphenytoin + omeprazole (n-18). The details are presented in **Fig. 2**.

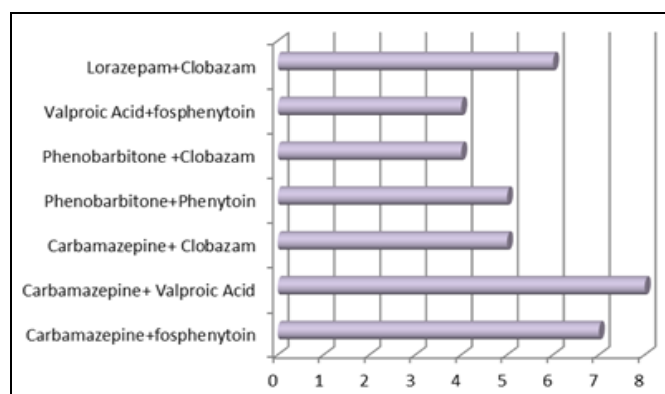


FIG. 1: AED - AED INTERACTIONS

DISCUSSION:

General Details of the Study Population: Studies conducted earlier also found that the boys (69.8%) predominance which is 2 folds greater than girls (30.2%) similar to the present study ⁵ whereas a study from the Netherlands, showed no significant differences between boys and girls ⁵. Maximum children (45.3%) belonged to age group of 6-10 year followed by (33%) the age group of 11-15 years in the previous similar studies which contradicts the finding of our study that we observed infants as the major epileptic patients ⁷.

Similar to our finding, 25.5% of children had a history of seizure disorder in the previous study ³. No children exhibited a family history of seizure disorder in our study but in a previous study found epileptic children born to mothers with epilepsy ¹². Study conducted by researchers from Oman, GTCS was the most observed seizure that contradicts finding of our study as we observed more of simple

and complex febrile seizures, which may be due to the racial, ethnic or genetic difference of various regions¹³.

AED Therapy: Standard textbooks and literature mentioned that the monotherapy is the goal pharmacological management of epilepsy and we also observed that most of our patients were treated with monotherapy^{4, 15}. We observed more of clobazam use which is in contradiction to an earlier study by Rusva A. Mistry *et al.*, where carbamazepine was found to be most commonly used AED as monotherapy⁵. Another study done by various researchers found phenobarbitone followed by phenytoin² and sodium valproate was most commonly used AED as mono-therapy^{2, 16}. The differences in the AED monotherapy choices may be because the seizure type majorly seen in all these studies were different than we observed among our study population. Also in the case of complex febrile seizures, diazepam/phenytoin/sodium valproate was used in the acute stage, and clobazam was used for maintenance therapy^{2, 5}. The previous study conducted by Hasan SS *et al.* found carbamazepine + valproate was the most commonly utilized combination, followed by valproate + lamotrigine⁸.

According to standard literature, approximately one-third of the epileptic patients do not respond to treatment with a single antiepileptic drug and combination of drugs are tried to control seizures. There are currently no clear guidelines for rational polytherapy although, in theory, a combination of drugs with different mechanisms of action may be useful¹⁷. Also in agreement with the guidelines, that new AEDs should be used as add-on therapy to an old AED-are the higher percentages we found for the new AEDs in combination therapy than in monotherapy^{18, 19}. Among the newer anti-epileptic drugs, levetiracetam was prescribed as a part of combination therapy. In a study carried out by Ackers *et al.*, to investigate the prescribing epidemiology in the United Kingdom, it was found that there was a rapid increase in newer AED (lamotrigine, topiramate, and levetiracetam) prescribing to children and adolescents than adults⁹.

AED Use in Disease Conditions Other than Epilepsy: In a study conducted by Nunes *et al.*, to

describe the neurological outcome of newborns with seizures it was found that meningitis (51%) was the etiology more frequently associated with seizures²⁰ which is similar to our study findings. We observed more of antibiotic use along with AEDs whereas in a study conducted previously, an antipyretic group of the drug was most commonly prescribed followed by antihistaminic and antimicrobials⁵, which again depends on the type of co-morbid conditions present with the seizure of the study population.

Drug-Drug Interaction: Though we identify some AED- AED interactions, all of those were not clinically significant events, so there was no change made during the treatment due to these interactions. All of those were theoretical only. The present study and previous studies showed that there is less risk of interaction of antimicrobials and antipyretics with various AEDs⁷.

CONCLUSION: Out of 294 children who were on antiepileptic medication only 64.96% responded to monotherapy while others required combination therapy. Simple febrile seizures were the commonest of epilepsy recorded. Monotherapy was preferred in most cases. Unlike previous studies, clobazam was the most frequently prescribed AED followed by phenytoin. Seizures were more common in boys and age group of one month-one year. Other disease conditions in which AEDs were used was meningitis, encephalitis, and ADEM. As observed in the current study, AEDs can interact with other AEDs and drugs of other classes, it is important for the health care professionals to monitor closely any children requires more than one AED to manage their epilepsy and to collect a detailed medication history while the epileptic children require any other drug regimen.

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