

**AN OBSERVATIONAL STUDY ON USE OF ANTIEPILEPTIC DRUGS IN PEDIATRIC
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ABSTRACT

Drug utilization study (DUS) is stepping stone to conduct drug use evaluation so that error in drug use can be observed and resources can be put to use in proper fashion. Seizure disorder is a generalized term which includes epilepsy, febrile seizure, single seizure all associated with excessive or uncontrolled discharge of neurons. Around 4-10% children suffer at least one seizure in first 16 years of life leading to prescription of Anti-epileptic drugs (AED's). The pharmacokinetics of AED's differs between pediatric and adults, 90% of people are not receiving AED's treatment due to various factors. **Results:** 132 pediatric patients prescribed with single or multiple doses of AED's. Midazolam (41%) was the most commonly prescribed Benzodiazepine, Phenytoin (25%) most commonly prescribed AED. Conventional AED's (95%) are more commonly prescribed in our study than Newer AED's (5%). **Conclusion:** Our study concluded that boys were more prone to seizure episode than girls. Phenytoin was the most used AED and Midazolam was most commonly used BZD. Midazolam monotherapy was used as first line of drug for management of seizure episode. Thus concluding study shows conventional AED's were still safe and effective in achieving seizure control.

KEYWORDS: Antiepileptic drug, Drug use study, Benzodiazepines, Pediatric.**INTRODUCTION**

Study on the pattern of drug usage has sustained in an unceasing manner since conference held on rational use of drug by World Health Organization (WHO) in Nairobi 1985 with the sole purpose of improvising the drug use practice by measuring drug usage in health care facilities that reflects prescribing pattern.^[1]

Drug utilization study is a technical approach that quantitatively and qualitatively aids in understanding the pattern of drug use showcasing a group or number of patient exposed to specific drug at a given point of time, helping research professional estimate the underuse/overuse/rational use of drug, evaluating drug's used other than indication and also in the evaluation of medicine for treating specific disease condition on the basis of recommended treatment guidelines.^[2]

According to WHO and ILAE (The International League Against Epilepsy) epilepsy being a burden to society and health care team, that requires management for longer

time duration necessitating study medication used to manage epilepsy by means of exploratory tools like drug use study which is a structured quality assurance method that studies a class of drug or an individual drug used within a population for a particular disease condition. Thus DUS (Drug Use Study) examines the drug prescribed, dose prescribed, administration, medication adherence and observed beneficial or adverse effects of therapy by which drug use pattern can be identified.^[3]

As per WHO *epilepsy* is defined as occurrence of transient paroxysm of excessive or uncontrolled discharge of neuron which may be due to number of causes leading to epileptic seizures.^[4] Seizure disorder is a general term that is usually used to include anyone of several disorder, including epilepsy, febrile seizure, possibly single seizures and symptomatic seizure secondary to metabolic infectious, or other etiologies (e.g.: hypocalcaemia, meningitis).^[5]

More than 50 million people worldwide are affected with epilepsy, making it one of the most common neurological diseases globally. It is estimated that there are more than 10 million cases of epilepsy in India.^[6] Around 4-10% of children suffer at least one seizure in the first 16 years of life. The incidence is highest in children below 3 years of age, with a decreasing frequency in older children.^[7] Approximately 8% of the general population will have at least one seizure and not have epilepsy.^[6]

The treatment of children with epilepsy differs from that of adults as biological half-life of AEDs (Anti-Epileptic Drugs) varies significantly from that of adults. AEDs are eliminated faster in children and hence dose adjustment is required. Also the cognitive effect of AED may be more serious than occasional seizures.^[8]

Around 90% of the people with epilepsy in developing countries are not receiving appropriate treatment due to cultural attitude, lack of prioritization, patients' ability to pay, poor health system infrastructure and inadequate supply of AEDs. Economic factors are important determinants of clinical decision making and the degree of effect depends on the country and health systems.^[9]

The basic ideology behind performing a drug use study on anti-epileptic drugs in special populations (paediatrics) was the high prevalence rate of seizures and use of medicines to control the same that act by varied unclear mechanism of action and lack of data on drug utilization pattern in paediatric population due to limited number of studies.

MATERIALS AND METHODS

- **Study Design:** Observational cross-sectional study.
- **Study Centre:** GMERS medical hospital, Gandhinagar.

Table 1: Study Characteristics

VARIABLES	MEAN \pm SD	RANGE
Age (years)	4.754 \pm 4.32	0.16-17
Weight (Kg)	14.127 \pm 8.49	1.9-52.7
Length of stay (Days)	4.772 \pm 4.001	1-39
Total drugs prescribed/patient/day	5.781 \pm 1.59	4-10.74
Total AEDs prescribed/patient/day	1.634 \pm 0.83	1-2.43

Utilization pattern

Table 2 shows different AEDs used in pediatric department. Midazolam was the most used BZD (Benzodiazepine) administered to 113 (41%) patients followed by clobazam in 37(13%) patients and diazepam in 2 (1%) patients. Phenytoin was the most used AED in 70 (25%) patients followed by sodium valproate in 35 (13%) patients, phenobarbital in 10 (4%) patients, levetiracetam and carbamazepine in 5(2%) patients.

- **Study period:** 6 months from date of ethics committee approval(October 2018 - march 2019) in which first 4 months was data collection period and the last 2 months were used for data analysis and report generation.
- **Study approval:** Study approval was obtained from human ethics committee, GMERS (Gujarat Medical Education and Research Society), Gandhinagar and KBIEC (K.B. Institute Ethics Committee), Gandhinagar.
- **Study population:** Pediatric population.
- **Sample size:** 132 patients.

❖ Inclusion criteria

All the prescriptions containing antiepileptic drugs written and used at pediatric ward site for in patients.

❖ Exclusion criteria

- ❖ Discharge medication order
- ❖ Out-patients prescription or prescription of patients who are not admitted at the study site.

❖ Study procedure

In- patients who met the study criteria were enrolled for assessing the drug utilization after obtaining their signature in informed consent forms. A designed data collection form was used to record all the necessary details like demographic details, complaints, diagnosis, time and duration of seizures, total number of drugs, and medication chart. Collected data was kept confidential and analysed statistically.

RESULTS

Total 1687 patients were admitted in paediatric ward over a period of 4 months, out of which data of 132 patients was collected who were prescribed with a single or multiple doses of antiepileptic drugs. The prevalence of seizure attack in patients admitted in IPD was found to be 7.82%.

Table 2: Different drugs prescribed in paediatric department of GMERS hospital, Gandhinagar during study period.

NAME OF DRUG	NO. OF PATIENTS	PERCENTAGE
Midazolam	113	41%
Phenytoin	70	25%
Sodium Valproate	35	13%
Levetiracetam	5	2%
Clobazam	37	13%
Phenobarbitol	10	4%
Carbamazepine	5	2%
Clonazepam	1	0.75%
Diazepam	2	1%
Lacosamide	1	0.75%

Use of AED according to formulation

The study uncovers 3 different types of formulations by which AEDs were administered that comprised of oral formulation, parenteral and nasal formulation 63%

patients were administered parenteral formulation followed by 36% patients who were administered oral formulation and only 1% patients were administered with nasal spray.

Table 3: Formulation of drugs used according to no. of patients in paediatric department of GMERS hospital, Gandhinagar during study period.

FORMULATION	NO. OF PATIENTS	PERCENTAGE
Oral	71	36%
Parenteral	123	63%
Nasal spray	1	0.75%

Comparison of mono-therapy, dual-therapy, triple-therapy and poly-therapy used according to age.

In patients of the age group 1 month to 2 years mono-therapy was widely used whilst in children of age group 2-12 years dual-therapy was observed for controlling seizures. Midazolam monotherapy was used as a first line drug for management of seizure attack. If seizure was not controlled with midazolam then phenytoin was

added. Midazolam+Phenytoin were the most used dual therapy. Chi square value of 23.14 was obtained on applying Chi square test between age group and type of therapy. P-value obtained was 0.0059 which indicates statistical significance.

Table 4: Showcase type of therapy used in different age groups given below.

Table 4: Type of therapy used according to age in pediatric department of GMERS hospital, Gandhinagar during study period.

Type Of Therapy	AGE GROUP				TOTAL	Chi Square Value	P-Value
	1 month to 2 years	2 years to 12 years	12 years to 16 years	16 years to 18 years			
Mono Therapy	20 (53%)	18 (23%)	1 (8%)	2 (67%)	41 (31%)	23.14	0.0059
Dual Therapy	13 (34%)	33 (42%)	5 (38%)	0 (0%)	51 (39%)		
Triple Therapy	3 (8%)	19 (24%)	6 (46%)	0 (0%)	28 (21%)		
Poly Therapy	2 (5%)	8 (10%)	1 (8%)	1 (33%)	12 (9%)		

*Mono therapy indicates treatment with one antiepileptic drug, dual therapy indicates treatment with two antiepileptic drugs, triple therapy indicates treatment with three AEDs and poly therapy indicates treatment with more than three AEDs.

Seizure treated with AED and BZD

The class of drug prescribed mostly for treating seizure attack was 'BZD only' (40%) which was recommended for all age groups.

Midazolam was maximum used BZD as majority of patients were admitted for febrile convulsion as the indication, which is managed using BZD only.

9 (7%) patients had been treated with 'AED only' therapy.

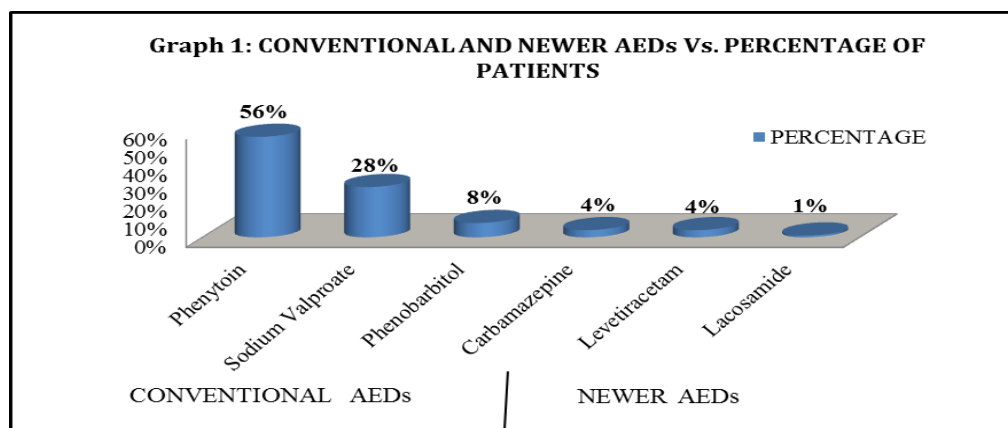
Table 5: Usage of AED and BZD within different age groups in pediatric ward at GMERS Hospital, Gandhinagar during study period.

THERAPY	AGE GROUP				TOTAL
	1 month to 2 years	2 years to 12 years	12 years to 16 years	16 years to 18 years	
BZD only	27	21	3	2	53 (40%)
AED only	2	6	1	0	9 (7%)
BZD + 1 AED	7	28	2	0	37 (28%)
BZD + 2 AED	0	18	6	1	25 (19%)
BZD + 3 AED	2	4	1	0	7 (5%)
BZD + 4 AED	0	1	0	0	1 (1%)

Utilization pattern of AED as conventional AEDs and newer AEDs

In the present study conventional AED are more 95 % frequently used to manage seizure as compared to newer AEDs 5%.

Phenytoin, a conventional AED is most widely used in 70 (56%) patients followed by sodium valproate 35 (28%) patients and levetiracetam being newer AED is used in 5 (4%) patient for management of seizures.



DISCUSSION

This study includes results of a total 132 study subjects whose medication order with AED have been analyzed for socio-demographic variables of subjects, disease condition diagnosed and used to assess drug utilization pattern of AEDs in the in-patient hospital setting of pediatric department in GMERS Gandhinagar. This study was designed and carried out with the intent of updating the data presented by other similar studies that have been carried out in pediatric population of India in the past.

Treatment with AEDs is the most widely and commonly approachable choice for the management of epilepsy and different types of seizures irrespective of age and gender. The selection of therapy and drug of choice varies from centre of healthcare as it is based upon the group of patients being treated, standard treatment guidelines that are followed and availability of drugs designed in the hospital formulary by the drug and therapeutic committee on the governing body.

Studying the drug utilization pattern of AEDs showed that midazolam 41% was the most commonly prescribed drug in majority of patients followed by phenytoin 25 %

and sodium valproate 13 %. This was in contrast to a study based in a tertiary care teaching hospital by George J et al where there was slight predominance 19.51% of phenytoin prescribed for study patients and 17.88% sodium valproate prescribed for study participants to treat epilepsy.^[9] The potential reason behind midazolam being majorly used is that majority of patients are admitted for febrile convulsion as the indication, which is managed using BZD as AEDs are not to be prescribed to manage such seizures as stated by therapeutic guidelines in text.

Our study uncovered that AEDs were prescribed majorly in the form of parenteral 63% followed by oral 36%. The study results did not correlate with results of any previous study conducted. Patients were prescribed AEDs in the form of parenteral because of the reason of ease of administration of drug, treatment compliance and medication adherence in order to prevent and manage seizure episode immediately after admission.

Almost 38.6 % of study participants received prescribed AED in dual therapy, while 31% patients received prescribed AED in mono-therapy. The results of the study varied with a hospital based study in India by

Lakshmi et al where 59% patients received prescribed AED in polytherapy and 41% patients received prescribed AED as mono-therapy.^[10] In our study there was statistically significant difference (P=0.0059) found between dual therapy, monotherapy, triple therapy and poly therapy, thus indicating that the usage of AED as dual therapy was more.

In our study maximum patients were prescribed with a conventional AED 95% while a few patients were prescribed with older + newer AED 5% and no patient was prescribed with only newer AEDs. A majority of previously conducted study on AED use like George J. et al confirmed that conventional AED 80.3% were prescribed more often in patients than older + newer AEDs 17%, indicating use of conventional AEDs over newer AEDs, The reason being that conventional AEDs are safe and effective in achieving seizure control and newer AEDs are more expensive and non-availability in government supply thus they are prescribed less frequently in low income countries.^[9]

CONCLUSIONS

Antiepileptic drug use study in pediatric ward gives an insight into current pharmacotherapy practices used to prevent seizure attack. Phenytoin was the most commonly used AED and midazolam was the most commonly used BZD. Midazolam monotherapy was used as a first line drug for management of seizure attack. If seizure was not controlled with midazolam then phenytoin was added. Midazolam+Phenytoin was the most used dual therapy. The drug clobazam which is a BZD is prescribed as a secondary drug for the management of febrile convulsion, prescribed consecutively for 3 days with recent episode or a past history of seizure due to fever. Conventional AEDs were used more as compared to newer AEDs.

This study showed that for a considerable number of patients, conventional AEDs were still safe and effective in achieving seizure control. Newer AEDs were not commonly prescribed may be due to higher cost and non-availability in government supply.

LIMITATIONS

Due to the reason of not being able to present at ward site for 24 hours patient prescribed with AED who were included in the study due to some unspecified reason were transferred to PICU or other ward in the hospital which eventually led to lack of follow up.

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