

# A Cross Sectional Study on Prescription Pattern of Antiepileptic Medication among Children of Southern Rajasthan in a Tertiary Care Teaching Hospital

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## Abstract

**Background:** Drug utilization studies are powerful exploratory tools for establishing the role of drugs in society and also effective methods for assessing the prescribing pattern of clinicians. Around 4-10% of children suffer at least one seizure episode at 16 years of age. Even after the availability of several Antiepileptic drugs (AEDs), choosing the correct drug with accurate dosing will produce seizure-free generation. Hence, this study aims to examine the prescription patterns of drugs in epileptic children.

**Methods:** This study was a cross sectional observational study. Children <16 years old visiting neurology department with a history of epileptic seizures and already on antiepileptic drug therapy were included in the study. The data comprised of demographic details, disease history, type of seizure, diagnosis, investigations done, along with prescribed medication noted in case record form. The total study duration was 13 months. .

**Results:** In this study, the maximum epilepsy encountering age in male and female children was below the 12-year age group, male predominance was higher than females (male 60.83% vs. female 39.16%). The majority of children were diagnosed with generalized tonic clonic seizures, 54.17%, followed by focal/or partial seizures, 39.17%. Sodium valproate 19.16%, carbamazepine 14.17%, oxcarbazepine 16.67%, and levetiracetam 13.33% were the most commonly prescribed single drug regimens for treating both types of seizures, followed by clobazam added as second and third adjuvant drug in resistant epilepsy to valproate 12.5%, oxcarbazepine 6.67%, and levetiracetam plus carbamazepine combination 5% respectively.

**Conclusion:** Monotherapy was majorly followed in 70% of pediatric patients for maintaining better patient compliance. Both old and new AEDs regimens are prescribed for maintaining the quality of life in patients.

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**Keywords:** Epilepsy; Antiepileptic Drugs; Drug Utilization; Children; Prescription.

## Introduction

Epilepsy is a disorder of the brain which is characterized by an enduring predisposition to generate seizures and by its neurobiological, cognitive, psychological, and social consequences (1). WHO estimates that, globally, 50 million people suffer from epilepsy and 80% of people with epilepsy live in developing and undeveloped countries. In India, 12 million people are suffering from epilepsy with a prevalence of 6.99% in rural areas and 5.48% in urban areas, and active epilepsy is 4.07 per 1000 children (2). Around 4-10% of children suffer at least one seizure episode in their early 16 years of age and the incidence rate gradually decreases as the age advances (3). Epilepsy incidences induce behavioral and cognitive problems impose lifelong serious effects in daily life (4). The aim behind antiepileptic drug use (AEDs) is to treat epilepsy to take control over seizures without causing any untoward medical reactions in patients. Patient

factors play pivotal role in choosing AED and its dose (5). In treatment, both conventional and new antiepileptic drugs have been prescribed (6). Adequate efficacy and well being have been accounted with both generations of AEDs (7). Almost 80% of seizures are effectively controlled with mono therapy and 20% of seizures with polytherapy in refractory cases (8, 9). Very limited data is available regarding favorable and unfavorable combinations of polytherapy (10). Clinicians need to be more focused on treating children and on making the right choice of a drug the right dose at the right time. It is very important therapeutic monitoring of drug involve in minimizing untoward adverse effects in children and make them active members of the society (6).

Drug utilization studies play an essential role in rational drug prescribing in order to minimize the possible adverse effects and improve patient compliance and quality of life. These drug utilization studies are powerful exploratory tools for establishing roles of drugs in society and also effective

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methods to assess the prescribing pattern of physicians (11). In order to produce a complication-free future generation of children, these types of prescription-based drug utilization studies play pivotal role. Till now, limited numbers of studies have been conducted on prescription pattern of antiepileptic drugs in children in other states (Gujarat) but not in of southern Rajasthan (11). Based on these reasons, the study was done to evaluate the prescription patterns of antiepileptic drugs in pediatric patients attending the neurology department of tertiary care teaching hospital.

## Methods

This study was a cross sectional observational study. It was conducted on epileptic children visiting the neurology department, tertiary care teaching hospital of southern Rajasthan, India. The duration of study was 13 months (August 2021 to September 2022). In this study we have not done any follow up of the patient and no data evaluated for the tapering drug dose, adverse drug reactions, and patient outcome. The study was started after the approval of the Institutional Ethical Committee (Ref: GU/HREC/2021/978). Epileptic children (male and female) below the age of 16 years being treated for various epilepsy types i.e., generalized tonic clonic seizures (GTCS), partial/or focal seizures, myoclonic, benignrolandic, absence seizures were included in the study. The patients with secondary causes of epilepsy due to head injury, cerebral palsy, stroke, metabolic disorders etc., were excluded. A filled written informed consent form was taken

from the patient's parents/guardians with their willingness to be involved in this study. Data was collected from OPD case papers and entered into specially designed patient data entry forms. Demographic details of patient (age, sex), type of seizure, frequency of seizure, diagnosis, investigations done, details of drug including its dose, duration and frequency were noted in case record form. The gathered data was compiled in Windows XL 7, Version 2007 to express the values in percentages and figures. The SPSS software was used to find out significant reduction in seizure episodes and their values were expressed in frequencies and percentage.

## Results

Table 1 shows gender, age, type of epilepsy and diagnostic tests performed among 120 children. Out of one twenty epileptic children, 73 were male (60.83%) and 47 were female (39.16%). The 6-10 year age group showed high epilepsy incidence 67 (55.83%) followed by the 0-5 year age group 45 (37.5%). The least epilepsy incidence was observed in the 11-16 year age group 8 (6.66%). On diagnostic test criteria, all the patients were examined with; EEG 82 (68.3%), EEG + CT scan 23 (19.16%), EEG+ MRI+CTscan 9 (7.5%), EEG+MRI 6 (5%). The majority of the children suffered from general tonic clonic seizure 65 (54.17%) followed by focal/partial seizure 47 (39.17%). Incidence rate of remaining epilepsy like myoclonic 3 (2.5%), primary generalized epilepsy 3 (2.5%), and benignrolandic 2 (1.67%) was noted minimal in this study.

Table 1. Gender, age, distribution of epilepsy and type of diagnostic test done in children.

Gender distribution of epilepsy		
Gender	No. of patients (n)	Percentage (%)
Male	73	60.83
Female	47	39.16
Total	120	
Age distribution of epilepsy		
Age in years	No. of patients (n)	Percentage (%)
0 to 5	45	37.5
6 to 10	67	55.83
11 to 16	8	6.67
Total	120	
Type of diagnostic test performed		
Test type	No. of patients (n)	Percentage (%)
EEG	82	68.33
EEG + MRI	6	5
EEG + MRI + CT scan	9	7.5
EEG + CT scan	23	19.17
Distribution of seizure types		
Seizure type	No. of patients (n)	Percentage (%)
GTCS	65	54.17
Focal /or partial	47	39.17
Myoclonic	3	2.5
Benginronaldic	2	1.67
Primary Generalized epilepsy (PGE)	3	2.5
Total	120	

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Table 1. Gender, age, distribution of epilepsy and type of diagnostic test done in children.

Type of drug therapy	No. of patients (n)	Percentage (%)
Mono therapy	84	70
Dual therapy	25	20.83
Triple therapy	11	9.17
<b>Monotherapy</b>		
<b>Drugs</b>	<b>No. of patients (n)</b>	<b>Percentage (%)</b>
SVP (Sodium valproate)	23	19.17
OCB(Oxcarbazepine)	20	16.67
LVT (Levetriacetam)	16	13.33
CBZ (Carbamazepine)	17	14.17
CLB (Clobazam)	5	4.17
PHE (Phenytoin)	2	1.67
<b>Type of drug therapy</b>		
PHB (Phenobarbitone)	1	0.83
<b>Total</b>	84	70
<b>Dual therapy</b>		
<b>Drugs</b>	<b>No. of patients (n)</b>	<b>Percentage (%)</b>
SVP + CLB	15	12.5
SVP + OCB	01	0.83
OCB + CLB	8	6.67
SVP+LVT	1	0.83
<b>Total</b>	25	
<b>Triple therapy</b>		
<b>Drugs</b>	<b>No. of patients (n)</b>	<b>Percentage (%)</b>
SVP + OCB + LVT	4	3.33
CBZ + LVT + CLB	6	5
SVP + CBZ + CLB	1	0.83
<b>Total</b>	11	

Table 3. Seizure episodes per month during the drug therapy.

<b>Before the drug therapy seizure episodes</b>	
Before t/t	no. of patients
1-2 episodes	53
3-5 episodes	60
6-8 episodes	6
> 8 episodes	1
Total	120
<b>After the drug therapy seizure episodes:</b>	
	no. of patients
Seizure free patients	68
1-2 episodes	45
3-5 episodes	7
6-8 episodes	0
> 8 episodes	0
Total	120

Table 2 shows the mode of drug therapy. In the table, we can see 84 patients were prescribed with monotherapy (70%), followed by dual therapy 25 (20.8%), and 11 patients (9.2%) were prescribed triple drug therapy. Sodium valproate 23 (19.2%), oxcarbamazepine 20 (16.6%), carbamazepine 17 (14.2%) and levetriacetam 16 (13.3%) were highly prescribed, followed by clobazam (4.2%) monotherapy drugs in this study respectively. Whereas, phenytoin 2 (1.67%), and phenobarbital 1 (0.83%) were the least prescribed monotherapy drugs. In dual drug therapy, 15 patients were prescribed with valproate+clobazam (12.5%) and 8 patients were prescribed oxcarbazepine+clobazam (6.6%) respectively. Only 4 patients were prescribed with sodium valproate + oxcarbazepine + levetriacetam triple drug combination (5%) respectively. The average number of antiepileptic drugs prescribed per prescription in this study was (1.3%) following WHO core prescribing indicators.

Table 3 shows the recovery status of seizure episodes before and after drug therapy. Among one twenty patients, 68 patients reported no seizure episodes, while 45 reported 1-2 episodes, 7 reported 3-5 episodes of epileptic seizures per month after treatment. A significant reduction in epileptic seizure episodes ( $P < 0.001$ ) was noted after applying the chi-square test respectively.

## Discussion

This study focuses on the utilization and outcomes of antiepileptic drugs' effect on reducing the frequency of seizures to improve the patient's quality of life. Treatment with AEDs in children should be aimed in such a way that controlling seizures with minimal side effects, possibly with monotherapy in a cost-effective manner. Drug utilization studies also help in understanding the rationality of drug usage in the target population and also encourage rational use of medicine (12). In this study, we found a greater prevalence of epilepsy in males at 60.83% than females at 39.16%, which is consistent with other studies (12, 13). This could be due to the proconvulsant activity of the male sex hormone testosterone (14, 15). The major epilepsy cases were found in the 6-10 year age group-55.8%, consistent with studies (11, 16). According to them, the majority of epileptic children were under the age of 12 years.

In the investigation of epilepsy, EEG was recommended to all 120 patients in this study. Only EEG was recommended in 68.33% of patients, which was high in number when compared with the Dave *et al.*, study where 49% respectively (11). Despite the availability of the most advanced investigational tools, i.e., CT scan, MRI, PET,

SPECT etc., in diagnosing epilepsy, chances of false positive or false negative results are greater. Hence, upon clinical suspicion, EEG is recommended as the gold standard diagnostic method to detect epilepsy (17). In this study we observed along with EEG some additional tests like CTscan+EEG 23%, MRI+CT scan 7.5% and MRI 5% were recommended as investigational tools respectively, depending on severity and physician choice. In our study, the most common type of seizure we observed; generalized tonic clonic seizure 54.17%, followed by focal/partial seizures 39.17%. According to the Amudhan *et al.*, survey report, it was confirmed GTCS is the most prevalent in the Indian population (18). The above mentioned values of GTCS suffers in our study were consistent with the findings of other studies conducted by sundaram *et al.*, (19). While Hasan *et al.*, reported in his study, focal seizures were the major epilepsy type in the Malaysian population (16). This could be due to ethnic, racial and genomic differences between populations. The myoclonic, benign rolandic, primary generalized epilepsy (PGE) were reported less as 2.5%, 1.67%, 2.5% in our study.

In the present study, the majority of the patients were treated with monotherapy 70%, followed by poly, i.e., double 20.83% and triple drug therapy 9.16%. Both conventional i.e., phenytoin (PHT), phenobarbital (PB), carbamazepine (CBZ), valproic acid (VPA) and newer antiepileptic drugs i.e., clobazam, levetriacetam, topiramate, lamotrigine, oxcarbazepine were prescribed in single and multiple drug formulations according severity and type of epilepsy (20).

In mono drug therapy we found sodium valproate 19.16% and carbamazepine 14.16% were extensively prescribed drugs in GTCS treatment following NICE guidelines (21). According to NICE guidelines, both drugs are added as 1st line drugs in epilepsy treatment. Due to broad spectrum activity towards various epilepsy types (except simple partial seizure) and a lower side effect profile, valproate is prescribed widely by physicians. These results were similar to previously conducted studies on the use of sodium valproate (22-24) and carbamazepine (11) as mono-drug therapies respectively. The patients who were unresponsive to valproate therapy clobazam were added as an adjuvant/dual drug to control GTCS in 12.5% of patients. This statement consistently matches with Johi *et al.*, conducted study on epileptic children at AIIMS medical college, Delhi, where clobazam was added to conventional antiepileptic drugs due to its broad spectrum activity over resistant focal seizures, generalized seizures with a less sedative nature, and economically cheap (25). Another UK-based study conducted by Mills *et al.*, on resistant epilepsy children also reported clobazam and topiramate effectively

decrease seizure frequency and improves the cognitive and behavioral performance in children during a one year observation period (26). Evidence supports combining AEDs with having a converse mechanism of actions given good results. Hence, a synergistic combination of valproate (acts on multiple targets including Na<sup>+</sup> channels) and clobazam (GABA receptor activator) was chosen in this study (27).

The focal/partial seizures subsequently came after GTCS in this study. Oxcarbazepine 16.66% and levetriacetam 13.3% were highly recommended mono-drug therapies in this study. According to pediatric epilepsy guidelines, carbamazepine is recommended as the 1st line drug to treat focal/partial seizures in children, due to frequent dosing, dose related adverse effects were more along with drug to drug interactions. Carbamazepine is prescribed less in daily practice (21, 28). Instead of conventional drugs, newer AEDs i.e., oxcarbazepine and levetriacetam were prescribed in this study. According to Suo et al., patients who were allergic to carbamazepine will tolerate oxcarbazepine better due to superior tolerability, less protein binding, and low enzyme induction rate by liver enzymes, strengthening use in daily practice to treat partial seizures in children (30). The patients who were unresponsive to oxcarbazepine monotherapy clobazam were added as an adjuvant drug in 6.6% of patients due to broad spectrum activity and synergistic combination to suppress partial seizures (26,27). Levetriacetam effectively suppresses the seizure threshold and induces anxiety and aggression. Contrary to carbamazepine, users induce dizziness and over sleep leads to patients discontinuing carbamazepine (28). This could be a reason behind physicians' choice to select levetriacetam for better patient compliance over carbamazepine in our study. Clobazam was added 5% as a third to carbamazepine plus levetriacetam combination in drug resistant GTCS and focal unresponsive epilepsy. Prescribing clobazam as an adjuvant drug due to broad spectrum and synergistic activity with other AEDs is consistently matching with Joshi R (25). The least prescribed drugs in our study were phenytoin 1.6% and phenobarbital 0.83%. Even though they were cost effective due to generating side effects, their use was limited (30, 31).

The average number of drugs prescribed per prescription in our study was 1.34%, more or less, 1.21%, matching with Dholakia et al., (32). A significant reduction of  $P < 0.001$  in epileptic seizure episodes is illustrated as; seizure free patients 56.6%, patients with 1-2 seizure episodes/month 37.5%, followed by patients with 3-5 episodes per month (5.8%) during their follow-up after AED therapy. The results were constantly matching with Dholakia et al., study

results illustrated in Table 3 respectively.

In our study, GTCS followed by focal/partial seizures were the most commonly observed epilepsy types in children. Physicians prescribed both conventional i.e., sodium valproate, carbamazepine in mono drug therapy to control GTCS in high numbers and clobazam added as second/ adjuvant drug to unresponsive cases of GTCS. Focal/partial seizures were treated with levetriacetam, oxcarbazepine and clobazam as mono and poly drug therapy (second and third drug) in resistant epilepsy cases. Significant reduction in seizure episodes was noted during the drug therapy. This will indicate increased utilization of new antiepileptic drugs in daily practice along with old drug regimens. Contemporary knowledge of AEDs is necessary in daily practice for better treatment.

### Conflict of interest

The authors declare that they have no conflict of interest in this work.

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