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DRUG UTILISATION STUDY OF ANTI-EPILEPTIC DRUGS IN PEDIATRIC PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT: Few studies are available to study the drug utilization pattern and adverse drug reactions of anti-epileptic drugs (AEDs) in paediatric population. Hence, this study was planned with the primary objective of studying the drug utilization pattern of anti-epileptic drugs in a tertiary care centre pediatric population. The secondary objective was to assess adverse drug reactions in the same population. Data from 214 pediatric patients visiting Neurology OPD was reviewed in this prospective, cross-sectional, non-interventional, observational study for 6 months. Patients aged 1 to 12 years, of either sex, diagnosed with epilepsy, and prescribed at least one anti-epileptic drug were included in the study. Sodium valproate was the most frequently prescribed anti-epileptic drug, followed by levetiracetam, carbamazepine, phenytoin, and clobazam. 49.07% of patients received monotherapy while 50.93% of patients received polytherapy. Out of the 39 adverse drug reactions (ADR) reported, the most common ADR was drowsiness (23.08%), followed by weight gain (17.95%), lethargy (15.38%), rash (10.26%), irritability (7.69%), decreased concentration, headache, vomiting (5.13%). The most common drug prescribed for generalized as well as focal seizures is sodium valproate, which is in accordance with National Institute for Health & Care Excellence (NICE) guidelines Prescribing the AEDs is a composite practice influenced by various factors. Thus, prescriptions that are audited at regular intervals will help physicians modify their prescription trend as per current recommended guidelines on managing pediatric epilepsy.

INTRODUCTION: Epilepsy, by definition, is a condition of recurrent unprovoked seizures. A seizure represents the uncontrolled, abnormal electrical activity of the brain that may cause changes in the level of consciousness, behavior, memory, or feelings [1].

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Epilepsy, as per the International League against Epilepsy (ILAE), is defined by at least two unprovoked seizures occurring more than 24 h apart or a single unprovoked seizure with a recurrence risk of at least 60% over the next 10 years or an identifiable epileptic syndrome [2].

Epilepsy is children's most common neurological disorder and remains a challenge to treat.[3] Worldwide, the prevalence of epilepsy in children ranges from 3.2-5.5 per 1000 in developed countries and 3.6-44 per 1000 in developing countries [4]. A study done by Murthy JM *et al.* in 7408 school-going children in South India, the

average annual incidence rate (AAIR) of epilepsy was 57.85 (95% CI 39.0–82.6) per 100,000 population [5]. Despite the increase in anti-epileptic drugs (AEDs), more than 25% of children with childhood epilepsy continue to have seizures. 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. Epidemiological studies reveal that approximately 150,000 children will sustain a first-time unprovoked seizure yearly and 30,000 will develop epilepsy [3]. There is currently no cure, so symptomatic pharmacological treatment remains the mainstay of therapy for epilepsy. Achieving complete seizure control is the most important objective in treating epilepsy. Also, patient tolerability of adverse drug effects is integral to successful treatment [6]. Treatment with AEDs in children should be aimed and focused in such a way that controlling seizures with lesser side effects, possibly with monotherapy, allows the child to contribute actively to society with cost-effective treatment [7]. However, the prescribing patterns of AEDs in children vary among countries because of differences in healthcare systems, cost of medicines, availability of drugs, and local and national epilepsy management guidelines [8].

Drug utilization study (DUS) was defined by World Health Organization (WHO) in 1977 as the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences [9, 14]. It mainly helps the healthcare system understand, interpret and improve medication prescription, administration and use [10]. However, there are few studies available in the literature for the drug utilization study of anti-epileptic drugs and adverse drug reactions of AEDs in pediatric population. Hence, we planned to do this present study with the primary objective of studying the drug utilization pattern of anti-epileptic drugs in a tertiary care center pediatric population. The secondary objective was to assess adverse drug reactions in pediatric patients on anti-epileptic drugs.

MATERIALS AND METHODS:

Study Design: The study was an observational, prospective, non-interventional study.

Study Site: The study was conducted in a Tertiary Care Hospital's Neurology Outpatient Department (OPD). The study was performed after receiving the necessary ethical clearance from the Institutional Ethics Committee. ECARP Reference No: ECARP/2016/51.

Study Duration: The study was carried out for a duration of 6 months, from October 2016 to March 2017.

Inclusion Criteria: Patients aged 1 to 12 years, of either sex, diagnosed with epilepsy, and who were prescribed at least one anti-epileptic drug were included in the study.

Exclusion Criteria: Children>12 years of age, patients/guardians not willing to participate in the study, acute cases of epilepsy, trauma (head injury), status epilepticus were excluded from our study.

Sample size Calculation: The sample size was designed based on the average number of pediatric patients visiting the Neurology outpatient department. The patient load of pediatric epilepsy cases in pediatric neurology outpatient department is approximately 20 per week, which is 80 patients in a month.

To represent 6-month patient population of 480, the sample size is calculated using a 95% confidence level and 5% confidence interval as per the sample size calculator, which equals 214 patients.

Data Collection: Data were collected from OPD case papers and entered in specially designed patient data entry forms. Demographic details of the patient, types of seizures, diagnosis, etiology of seizures, investigations done, AEDs prescribed, concomitant medications, and adverse drug reactions (ADR) were noted in a restructured case record form. The causality assessment of ADR was assessed by using Naranjo's algorithm [11].

Informed Consent: Patients fulfilling the inclusion and exclusion criteria were included in the study. Patients / Legally Authorized Representatives (LAR) were informed about the nature of study. Written informed consent from the patient's parent/guardian if child < 7 years and child assent statement if age > 7 years was taken.

Statistical Analysis: Descriptive statistics were used to summarize the data. Microsoft Excel version 2016 was used for statistical analysis and graphs and tables.

RESULTS:

Age and Gender Distribution of Patients: Out of 214 patients enrolled in the study, the most commonly affected age group was 5-8 years (n=88, 41.12%) followed by 9 –12 years group (n=68, 31.78%) and 58 patients were in the 1– 4 years group (n=58, 27.1%). The patient population's mean age ± Standard deviation (SD) was 6.71± 3.06 years. The age and gender distribution of the patient population is shown in **Fig. 1**. 46.26% of the patients were females and 53.74% were males, thereby the male: female ratio was 1.16:1.

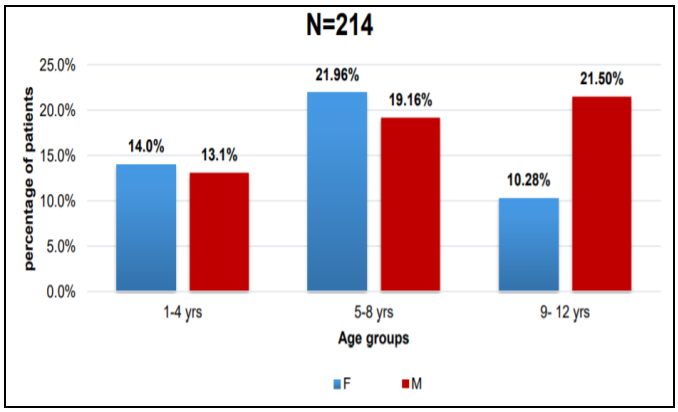

FIG. 1: AGE AND GENDER DISTRIBUTION OF PATIENTS. Blue bars represent male population. Red bars represent female population. Total number of patients N=214.

Types of Seizures Observed: The most common seizure type observed was generalized seizures in 145 patients (67.76%), followed by complex partial seizures in 48 patients (22.43%) and simple partial seizures in 21 patients (9.81%).

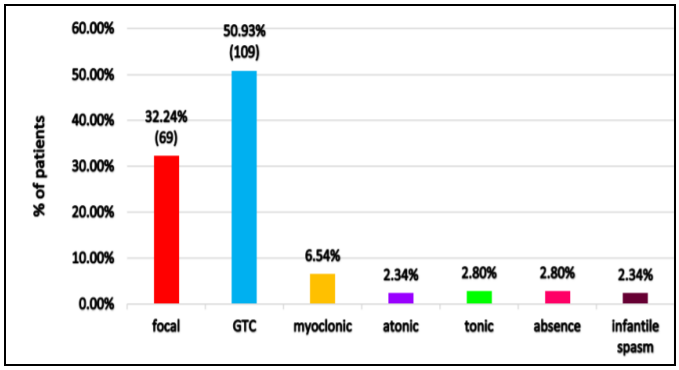

FIG. 2: PERCENTAGE DISTRIBUTION OF PATIENTS SUFFERING FROM DIFFERENT TYPES OF SEIZURES. GTC= Generalised tonic-clonic. The total number of patients N=214.

Simple and complex partial seizures are focal types of seizure. Generalized seizures are further divided into generalized tonic-clonic (GTC), myoclonic, atonic, tonic, absence, or infantile spasms. Generalised tonic-clonic (GTC) was most common seizure type (n=109, 50.93%) followed by focal seizures (n=69, 32.24%), myoclonic seizures (n= 14, 6.54%), tonic seizures (n=6, 2.80%), absence seizures (n=6, 2.80%), atonic seizures (n=5, 2.34%) and infantile spasms (n=5, 2.34%).

Etiology of Seizures: Most common etiology was idiopathic (n= 88,41.12%) followed by perinatal insult (n = 79, 36.92%). Infective etiology was seen in 34 patients (15.89%) out of which meningitis (n = 15, 44.12%) was the most common reason for infective etiology. 7 (3.27%) patients had an anatomical etiology, genetic causesin 6 (2.80%) cases and among genetic causes, tuberous sclerosis was the most common cause (n = 3) **Fig. 3**, **Table 1.**

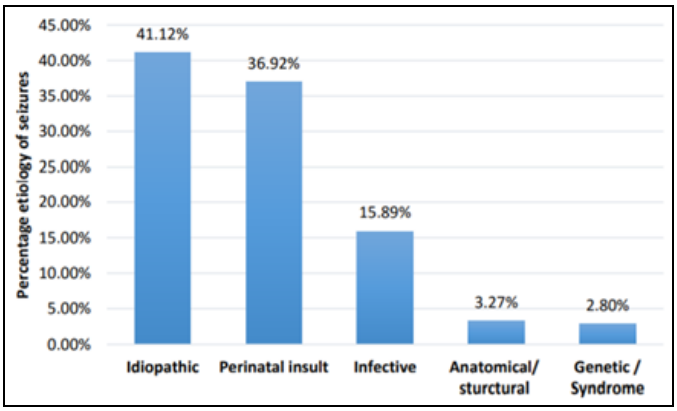

FIG. 3: PERCENTAGE ETIOLOGY OF SEIZURES. Total number of patients N=214.

TABLE 1: CAUSES OF INFECTIVE ETIOLOGY

Infective causes	Percentage of patients (number of patients)
Neurocysticercosis	23.53% (8)
Meningitis	44.12% (15)
Encephalitis	29.41% (10)
Temporal lobe abscess	2.94% (1)
Total	100% (34)

The table shows the infective causes of seizures. The total number of patients was 214.

Investigations Done: Out of 214 patients, Electroencephalogram (EEG) was done in 205 patients (95.79%), while Magnetic Resonance Imaging (MRI) was done in 191 patients (89.25%), Computed Tomography (CT) scan was done in 29 patients (13.55%) and Therapeutic Drug

Monitoring (TDM) in 96 patients (44.86%). EEG was abnormal in 53.27% of patients, TDM levels were high in 7 patients (7.29%), and low levels were observed in 29 patients (30.21%).

Prescribing Pattern of Anti-epileptic Drugs: The 214 prescriptions analyzed in the study had 697 drugs, out of which 358(51.36%) drugs were anti-epileptic drugs and 339 (48.64%) were other concomitant drugs.

The average number of drugs prescribed was 3.26 ± 1.07 (Mean ± SD) per prescription, and the average number of anti-epileptic drugs prescribed was 1.67 ± 0.77(Mean± SD) per prescription. A total 358 AEDs were prescribed in 214 patients, of which sodium valproate (n=166, 46.37%) was the most frequently prescribed drug, followed by levetiracetam (n= 45, 12.57%). The third most commonly prescribed drug is carbamazepine (n = 42, 11.73%), phenytoin was prescribed to 37 (10.34%), clobazam to 34 (9.50%), phenobarbitone and clonazepam were prescribed to 7 (1.96%) patients each.

Lamotrigine was prescribed to 6(1.68%) patients, 5(1.39%) patients were prescribed vigabatrin and oxcarbazepine, topiramate and nitrazepam each were prescribed in 3 (0.84%) patients.105 (49.07%) received monotherapy, and 109 (50.93%) received polytherapy **Table 2.**

Total AEDs prescribed were 358, of which 296 (82.68%) conventional AEDs were prescribed, i.e., phenytoin, carbamazepine, sodium valproate, phenobarbitone & benzodiazepines, while a total 62 (17.32%) newer AEDs were prescribed.

TABLE 2: PRESCRIBING FREQUENCY OF AEDS

	Prescribing Frequency			
Anti-epileptic drug	**Monotherapy**	**Polytherapy**	**Total**	**Percentage of patients**
Sodium valproate	70	96	166	46.37%
Levetiracetam	3	42	45	12.57%
Carbamazepine	7	35	42	11.73%
Phenytoin	18	19	37	10.34%
Clobazam	-	34	34	9.50%
Phenobarbitone	7	-	7	1.96%
Clonazepam	-	7	7	1.96%
Lamotrigine	-	6	6	1.68%
Vigabatrin	-	5	5	1.39%
Oxcarbazepine	-	3	3	0.84%
Topiramate	-	3	3	0.84%
Nitrazepam	-	3	3	0.84%
Total	105	253	358	100.0%

The table shows the prescribing frequency of various anti-epileptic drugs given as monotherapy and polytherapy. The percentage of patients receiving these drugs is also mentioned.

Out of the 109 patients receiving polytherapy, 78(36.45%) patients were on the two-drug combination, 27(12.62%) patients were on 3 drug combination and 4 (1.87%) patients were on 4 drug combination therapy. 11 different combinations of 2AEDs were prescribed.

Amongst these, combination of sodium valproate + carbamazepine (CBZ)' was most commonly prescribed (n=18, 23.08%), followed by combination of sodium valproate + levetiracetam & sodium valproate + clobazam' in 14 patients each (n=14, 17.95%) **Fig. 4.**

11 different combinations of 3 drugs were prescribed.

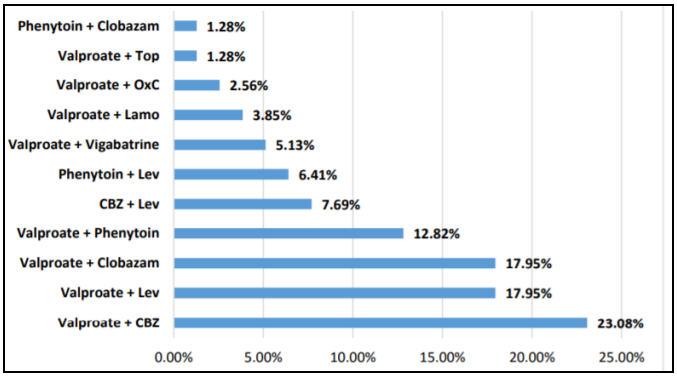

FIG. 4: PRESCRIBING PATTERN OF 2 DRUG COMBINATIONS OF AEDS. The 2 drug combination of AEDs is shown as a percentage of patients in whom the combination was prescribed. CBZ = carbamazepine, Lamo = lamotrigine, Lev= levetiracetam, OxC = oxcarbazepine, Top = topiramate.

Most common was combination of sodium valproate + clobazam + clonazepam' (n=7, 25.93%) followed by 'sodium valproate + levetiracetam + clobazam" combination (n = 4, 14.81%) **Fig. 5.**

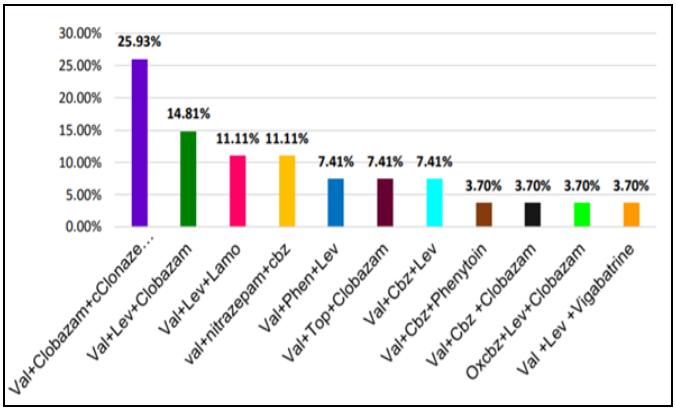

FIG. 5: PRESCRIBING PATTERN OF 3 DRUG COMBINATIONS OF AEDS. The 3 drug combination of AEDs is shown as a percentage of patients in whom the combination was prescribed. Cbz = carbamazepine, Lamo = lamotrigine, Lev= levetiracetam, Oxcbz = oxcarbazepine, Phen = phenytoin, Top = topiramate, Val = sodium valproate.

Concomitant Medications: A total number of 339 concomitant medicines were prescribed to 214 patients, calcium supplements were the most frequently prescribed drugs (n= 212, 62.54%), and the second most common was multi-vitamin supplements (n = 49, 14.45%). Other drug prescribed were baclofen (n=21, 6.19%), risperidone (n=13,3.83%), iron salts (n=9, 2.65%).

Adverse Drug Reactions (ADR): Change in anti-epileptic drug therapy was observed in 47 (21.96%) prescriptions, the most common reason being uncontrolled seizures 27(57.45%), followed by adverse drug reactions (n=11, 23.40%), breakthrough seizures (n=5, 10.64%) and low TDM (n=4, 8.51%).

Most common ADR was drowsiness (n = 9, 23.08%), followed by weight gain (n = 7, 17.95%), lethargy (n = 6, 15.38%), rash (n = 4, 10.26%), irritability (n = 3, 7.69%), decreased concentration, headache, vomiting (n=2, 5.13%). In our study as per the Naranjo scale, it was found that 7.69% ADRs belonged to 'doubtful' category, 19 (48.71%) ADRs belonged to the 'possible' category, 16 (41.06%) ADRs were in probable' category and 1 (2.56%) was a 'definite' ADR.

TABLE 3: NUMBER AND PERCENTAGE OF ADRs

Adverse Drug Reaction	Number of ADRs	Percentage of ADRs
Drowsiness	9	23.08%
Weight gain	7	17.95%
Lethargy	6	15.38%
Rash	4	10.26%
Irritability	3	7.69%
Decreased concentration	2	5.13%
Headache	2	5.13%
Vomiting	2	5.13%
Learning Disability	2	5.13%
Cerebellar ataxia	1	2.56%
Giddiness	1	2.56%
Total	39	100.0%

The table shows the different adverse drug reactions observed, the number of ADRs and the percentage (expressed in terms of total number of ADRs)

TABLE 4: CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS ACCORDING TO NARANJO'S SCALE

Naranjo score	Number of ADR	Percentage of ADR	Causality (total number of ADR)
0	3	7.69%	Doubtful (3)
1	3	7.69%	Possible (19)
2	4	10.26%	
3	5	12.82%	
4	7	17.95%	
5	2	5.13%	Probable (16)
6	8	20.51%	
7	3	7.69%	
8	3	7.69%	
9	1	2.56%	Definite (1)
Total	39	100%	

DISCUSSION: Pediatric patients are anatomically and physiologically different from a normal healthy adults in terms of body weight and surface area. The physiological systems are also in a growing phase that contributes to differences in the rate and extent of drug absorption, metabolism, excretion (pharmacokinetics), and pharmacodynamic effect compared to normal healthy adults. Thus, it is important to monitor dose, dosage formulation, route(s) of administration, and ADRs for treating and controlling epilepsy in pediatric patients [12].

In the present study, amongst 214 patients, the most commonly affected age group and the average age were 5-8 years (41.12%) and 6.71± 3.06 years, respectively. However, according to Mistry *et al*, the maximum number of patients (45.3%) belonged to the age group 6-10 years, and the mean age of the study population was 8.64 ± 3.7 years [13]. In a study by Dave and Trivedi, the majority of the patients belonged to the age group 6 to10 years, and the mean age of the patient was 9.14±3.65 years [14].

In this study, 67.76% of patients had generalized seizures. Also, complex partial seizures were more common, noted in 22.43% of patients, and simple partial seizures were noted in 9.81% of patients. Out of the generalized seizures noted in our study, the generalized tonic clonic (GTC) seizure was the most common, followed by myoclonic, absence, tonic type, infantile spasms, and atonic seizures. These findings are comparable to that of Maity and Gangadhar [16]. Dave and Trivedi also reported generalized tonic-clonic seizure as the most commonly observed seizure present in 55% of patients [14]. Khosdel Z *et al.* also observed that 60% of patients had generalized seizures, and 48% had generalized tonic-clonic seizures [9]. A generalized tonic-clonic seizure is the most common type seen in patients with epilepsy [15]. Our study's most common seizure etiology was diopathic followed by perinatal insult and infective etiology. This was similar to the studies done by Mistry *et al*, Maity and Gangadhar, which showed that most patients had no specific cause of seizure [13, 16]. The most common infective etiology in our study was meningitis. The American Academy of Neurology guideline for epilepsy recommended EEG as a part of routine neurodiagnostic evaluation for diagnosis and also suggests diagnostic use of CT and MRI.

In our study, EEG was done in 95.79% of patients, while MRI and CT scans were done in 89.25% and 13.55% of patients, respectively. In the Maity and Gangadhar, Mistry *et al*, Dave, and Trivedi study, EEG was done in 86.18 %, 83.3%, and 100% of patients, respectively [13, 14, 16]. MRI and CT scans were carried out in 21.4% and 10.5% of patients, respectively. In a study by Dave and Trivedi, MRI and CT scans were done in only 16% and 42% of patients, respectively [14].

TDM was done in 44.86% of patients, out of which TDM levels were normal in 62.50%, high in 7.29%, and low levels were observed in 30.21% cases. Maity and Gangadhar reported TDM done in only 20.5% patients [16]. This may be because some researchers have advocated serum drug level measurements only in special situations and not for routine clinical practice. In our study, sodium valproate was the most frequently prescribed anti-epileptic drug, followed by levetiracetam, carbamazepine, phenytoin, and clobazam.

This is in contrast to a study by Maity and Gangadhar, where carbamazepine was the most commonly prescribed drug, followed by sodium valproate [16]. Also, Dave and Trivedi reported carbamazepine as the most commonly prescribed drug, followed by sodium valproate [14]. However, in a study by Khosdel Z *et al.* and Hasan *et al.*, sodium valproate was the most commonly prescribed AED [3, 9]. In a systematic review by Egunsola O *et al.* to determine global AED utilization prevalence, sodium valproate was the most frequently prescribed AED in children in most countries [8]. Because of its broad spectrum of anticonvulsant activity, sodium valproate has the broadest profile of clinical indications. It is also well tolerated and has a favourable tolerability profile. Its efficacy in both focal and generalized seizures and epilepsy syndromes, especially in paediatric population, has been widely and accurately validated with randomized controlled trials and observational studies [17]. National Institute for Health & Care Excellence (NICE) guidelines for treating pediatric epilepsy recommend sodium valproate for patients with generalized seizures and carbamazepine for focal seizures [18]. This could be why sodium valproate is our study's most commonly prescribed drug. The second most common drug was levetiracetam, this shows that

the use of newer AEDs is on the rise, which has been attributed to the better side effects profile of newer AEDs. In our study, 17.32% of newer AEDs were prescribed and used mainly to add to conventional AEDs. The newer AEDs like levetiracetam, topiramate, lamotrigine, vigabatrin, oxcarbazepine, and benzodiazepines like clobazam were not on the hospital schedule, and thus, this could be the reason that they were prescribed to a lesser extent.

When single drug therapy does not provide adequate seizure control, polytherapy is necessary to achieve the goal of treatment. In our study, 49.07% of patients received monotherapy, and 50.93% received polytherapy. In patients receiving polytherapy, the percentage of patients on 2 drugs, 3 drugs and 4 drugs combination therapy was 36.45%, 12.62%, and 1.87%, respectively. Our findings were in contrast with those reported by Hasan *et al.*, Maity and Gangadhar, where the majority of patients were on monotherapy [3, 16]. Amongst patients on monotherapy, sodium valproate was the mostcommonly prescribed AED followed by phenytoin, carbamazepine, phenobarbitone, levetiracetam. However, Mistry *et al,* Maity and Gangadhar reported that carbamazepine is the most commonly used monotherapy [13, 16]. The most common 2 drug combination was sodium valproate plus carbamazepine, similar to Maity and Gangadhar [16]. The most common 3 drug combination was sodium valproate plus clobazam plus clonazepam, which is in contrast to Maity and Gangadhar. The most common 3 drug combination was carbamazepine plus phenytoin and lamotrigine [16].

The most common ADR in our study was drowsiness, and the most common drug involved in ADR was sodium valproate, followed by carbamazepine. This was done by Mistry *et al.* in which the most common ADR was irritability, drowsiness, and the most common drug involved in ADR was sodium valproate, followed by carbamazepine [13]. From this study, we observed that prescribing of the AEDs is a composite practice influenced by various factors considering the type and subtype of an epileptic seizure, evaluating therapy regularly, giving instructions to caregivers, parents and guardians about intended use, different practicing guidelines *etc*. These are a few factors that are a part of the drug utilization study. Thus, prescriptions that are audited at regular intervals will help physicians modify their prescription trend as per current recommended guidelines on managing pediatric epilepsy.

Limitations of Study: This study was a cross-sectional study; hence we were unable to understand long-term changes in prescription patterns. Our study was done at a tertiary care hospital where most patients were from low socioeconomic status. So, drugs that were on hospitals' schedules were preferentially prescribed. Hence, we did not take up to study the cost of therapy of AEDs. We did not assess the impact of anti-epileptic drug therapy on health-related quality of life. Measuring quality of life could have given better idea regarding treatment effectiveness.

CONCLUSION: The most common drug prescribed for generalized and focal seizures was sodium valproate, by NICE guidelines. Levetiracetam was the most commonly prescribed new drug. 49.07% of patients were on monotherapy and 50.93% patients received polytherapy, out of which 36.45% were on the two-drug combination. Sodium valproate plus carbamazepine was the most common two-drug combination prescribed. The most common ADR in our study was drowsiness, and the most common drug involved in ADR was sodium valproate, followed by carbamazepine.

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CONFLICTS OF INTEREST: None.

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