

PRESCRIBING PATTERN OF ANTIEPILEPTIC DRUGS IN PEDIATRIC PATIENTS AT A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Objectives: Epilepsy is one of the common neurological conditions worldwide.

Methods: The observational, continuous, prospective, and single-center study was carried out to evaluate prescribing pattern of antiepileptic drugs (AEDs) in pediatric patients at a tertiary care teaching hospital of Gujarat for a total duration of 18 months. Patients were followed up monthly for the period of 3 months to evaluate seizure freedom, breakthrough seizure, and change in the AEDs, add-on therapy, treatment adherence and ADRs. Rationality was assessed for selection of drug and selection of the right dose according to recent guidelines.

Results: Majority of patients in the age group of 7-9 years with mean age of 6.83 ± 3.09 years. Male-to-female ratio was 1.3:1. Total 73 AEDs were prescribed to pediatric epilepsy patients after diagnosis. Thirty-seven (69.80%) patients were prescribed AED on visit as monotherapy and 16 (30.20%) patients were prescribed polytherapy. Sodium valproate (77.36%) was most commonly prescribed AED followed by levetiracetam and carbamazepine. Most of AEDs were prescribed according to NICE guideline and by generic name.

Conclusion: Conventional AEDs are still used as first line of treatment for pediatric epilepsy patients, although newer AEDs also frequently prescribed as add on or primary drug. Low birth weight, NICU admission, and non-compliance to treatment are associated with breakthrough seizures.

Keywords: Antiepileptic drugs, Pediatric patients, Adherence, Breakthrough seizures.

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INTRODUCTION

Epilepsy is one of the common neurological conditions worldwide with the prevalence rate of 4.15-7.03 per 1000 population in India. The incidence of epilepsy is quite high in the pediatric population with 30% of children having their first episode of seizure before age of 4 years [1].

The mainstay of management of epilepsy is antiepileptic drugs (AEDs). Despite more than 20 approved AEDs, about 30% of patients are refractory to treatment. Pharmacoresistant epilepsy is a major health problem, associated with deteriorating quality of life, increased morbidity and mortality, and accounting for much of the economic burden to epileptic patients [2]. In recent studies of children and adults with uncontrolled seizures, 64% used polytherapy with two or more AEDs [3].

Various guidelines for management of epilepsy have been updated recently according to efficacy and safety profile of first and second-line AEDs. Hence, the selection of appropriate AED with the right dose for the right patient is very crucial.

The WHO definition of adherence has been universally accepted; the extent to which a person's behavior - taking medication, following a diet, and or executing lifestyle changes - corresponds with the agreed recommendations from a provider [4]. In developed countries, non-adherence to the treatment of chronic diseases ranges from 30% to 50%, and this rate is even higher in developing countries [4]. Most interesting is that 60% of treated patients stop taking the medication without relapse within 2-5 years of treatment [5]. Non-compliance significantly increases the risk of seizures and status epilepticus, hospitalization and also lead to developmental delay, and behavioral abnormalities in pediatric epilepsy patients. Therefore, finding accurate and standardized measurements of medication adherence are of great importance [6].

Developing countries have limited funds for health care so it becomes very important to prescribe drugs rationally so, to utilize available

funds optimally. More studies are required to evaluate their use as first-line AED for children with epilepsy; caution must be exercised for possible drug interactions with conventional AEDs before using them as an adjunct or as an add-on therapy.

Very few studies conducted previously in this hospital regarding the antiepileptic drug use in pediatric epilepsy patients. Hence, the present study was conducted to evaluate the prescribing pattern of AEDs and treatment adherence in pediatric epileptic patients.

METHODS

The observational, continuous, prospective, and single-center study was carried out to evaluate prescribing pattern of AEDs in pediatric patients in the Department of Pediatrics at a tertiary care teaching hospital of Gujarat. The study was conducted for a total duration of 18 months. Patients were enrolled in the study for 15 months and monthly follow-up was carried out for 3 months. Study protocol was approved by Institutional Ethics Committee (Ref. No.EC/Approval/51/2020). Participants were enrolled as per inclusion and exclusion criteria. All the patients of either gender willing to give written informed consent or assent, diagnosed with epilepsy attending pediatric epilepsy OPD for first time, and prescribed AEDs were included in the study.

Patients were diagnosed based on careful history taking, physical examination, as well as neurological examination (e.g., Electroencephalography) by a pediatrician. The detailed information of the patients was obtained from patients' attendants and recorded in preformed case record form (CRF). CRF was pretested and pre-validated. Demographic details, anthropometric measurements, present, personal, and past history, birth and immunization history, specific investigations, for example, EEG, CT, and MRI, diagnosis, and prescribed AEDs and concomitant drugs (i.e., dose, duration, route, form, frequency, brand name, and generic name) collected and entered in CRF. Patients were followed up monthly for the period of 3 months

to evaluate seizure freedom, breakthrough seizure, change in the AEDs, add-on therapy, treatment adherence, and ADR monitoring.

Data were entered in Microsoft Excel 2019. Descriptive statistics (mean, standard deviation, median, and ratio) were used to describe continuous variables. Frequency statistics (number and percentage) were used to describe categorical variables. Chi-square test was used to determine significant factors associated with breakthrough seizures. For analyzing the association between treatment adherence 95% and breakthrough seizures, Fisher's exact test was used. Association between non-compliant and breakthrough seizures was analyzed by Pearson correlation coefficient test using online statistical test calculator. $p < 0.05$ was considered statistically significant.

Rationality assessment of prescribed AEDs done according to the recent ILAE (International League Against Epilepsy) guideline 2017, NICE (National Institute for Health and Care Excellence) guideline (updated in 2020), and recent IAP (Indian Association of Pediatrics) guidelines [7-9]. Rationality was assessed for selection of drug and selection of right dose.

RESULTS

This observational, continuous, prospective, and single-center study was carried out at the department of pharmacology and outpatient department of pediatrics at a tertiary care teaching hospital. A total of 53 pediatric patients presented to the pediatric epilepsy outdoor patient department first time and prescribed AEDs were enrolled in the study. Out of 53 patients enrolled, 51 patients (96.22%) completed 1st follow-up, 46 patients (86.79%) completed their 2nd follow-up and 29 patients (54.17%) completed their 3rd follow-up.

Demographic details with lifestyle/behavioral characteristics

Majority of patients in the age group of 7-9 years with mean age of 6.83 ± 3.09 years. Male-to-female ratio of the patients was 1.3:1. Mean weight was 19.79 ± 8.46 kg. About 84.90% of the patients were from an urban residential area. About 60.38% of the patients were fully immunized and 28.30% were partially immunized (Table 1).

Most of patients presented with a history of seizures with/without frothing from the mouth and/or body movements. The most

common complaints associated were developmental delay (35.84%), hyperactivity (16.30%), and involuntary movements (14.30%) on the first visit.

History of hospitalization for convulsion, dengue, diarrhea, jaundice, meningitis, acute viral encephalitis, fever, and similar complaints was present in 14 (26.41%) patients. History of tuberous sclerosis and neurofibromatosis-1 were also present in 3.77% each.

Out of 53 patients, eight patients were having a past history of at least one seizure attack in their 1st week of life, 19 patients were having the first attack at the age group between 2nd week to 2 years, whereas 26 patients had the first attack between the age of 3-12 years. Majority of patients had asleep duration of 10 h/day.

Out of 53 patients, 49 (92.46%) patients had a history of hospital delivery, and 3 (5.66%) patients had a history of home delivery. About 47 (88.67%) patients were born at full-term, whereas 5 (9.43%) patients were born preterm. Cry soon after birth was present in 43 (81.13%) patients. Forty-one (77.35%) patients were born through normal vaginal delivery and 11(20.75%) patients had a history of lower segment cesarean section (LSCS). Twelve (22.65%) patients had a history of admission in neonatal ICU after birth.

Pediatric epilepsy patients were investigated mainly for electroencephalography (EEG), hearing assessment, and ophthalmic fundus examination. Electroencephalography was done in 92.45% of patients, out of which 64.50% of patients were having abnormal EEG. In EEG, common findings noted were neuronal hyperexcitability (either generalized or from a particular lobe of the brain), symmetrical and synchronous 8-10 Hz alpha waves, 3 Hz spike and wave pattern, hyperthymic pattern, etc.

Most common diagnosis of the patients in pediatric epilepsy OPD was generalized tonic-clonic seizure (GTCS) and GTC epilepsy (52.83%), followed by remote symptomatic epilepsy (RSE) (20.75%), focal epilepsy (13.20%), complex febrile convulsions (5.66%), unprovoked seizures (3.77%), childhood absence epilepsy (1.88%), and partial epilepsy (1.88%).

Total 73 AEDs were prescribed to pediatric epilepsy patients after diagnosis. Thirty-seven (69.80%) patients were prescribed AED on visit as monotherapy and 16 (30.20%) patients were prescribed polytherapy.

Most commonly prescribed AED in pediatric epilepsy patients was sodium valproate 77.36% followed by levetiracetam 26.42% and carbamazepine 16.98% (Fig. 1). Conventional AEDs were prescribed

Table 1: Demographic details with lifestyle/behavioral characteristics of pediatric epilepsy patients at Civil Hospital Ahmedabad (n=53)

Variables	Study participants, n (%) (n=53)
Age group (years)	
0-5	17 (32.07)
6-12	36 (67.93)
Gender	
Male	30 (56.60)
Female	23 (43.40)
Male-to-female ratio	1.3:1
Anthropometric measurements on the visit (mean±SD)	
Weight	19.79±8.46 kg
Height	112.02±20.97 cm
Head circumference	49.26±4.79 cm
H/O allergy	
Yes	4 (7.54)
No	49 (92.46)
Immunization history	
Unimmunized	6 (11.32)
Partially immunized	15 (28.30)
Fully immunized	32 (60.38)
Family history	
Positive family history	13 (24.52)
Positive parental consanguinity	3 (5.66)

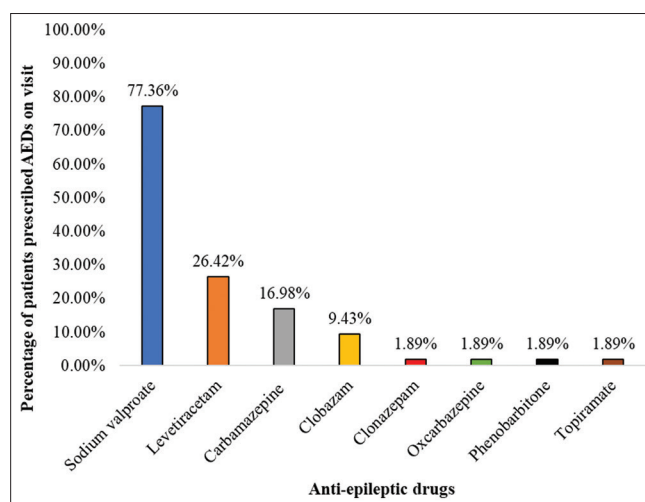


Fig. 1: Analysis of prescribed anti-epileptic drugs on the first visit (n=53)

in 33 (62.26%) patients, 4 (7.54%) patients received newer AEDs, whereas 16 (30.20%) patients were prescribed combination of both conventional + newer AED combinations (Table 2). Newer AEDs prescribed were levetiracetam, oxcarbazepine, topiramate, etc.

Out of 16 patients who received polytherapy, 12 patients received a combination of two AEDs, whereas four patients received combination of three AEDs. Most commonly prescribed AED combinations on visit were valproate + levetiracetam (7.54%), valproate + levetiracetam + carbamazepine (5.77%), levetiracetam + clobazam (5.77%), etc. All AEDs were prescribed by oral route. About 65.75% AEDs were prescribed by tablet dosage form and 34.25% by syrup dosage form. Analysis of mean dose of prescribed AEDs is given in Table 3.

Out of 73 AEDs prescribed on visit, most common frequency was twice daily (84.93%) followed by thrice daily (9.58%) and once daily (5.47%).

WHO core indicators for drugs prescribed

1. Average number of drugs prescribed per encounter was 3.71.
2. Percentage encounter with antibiotics were 0%.
3. Average number of drugs prescribed as injections was 0%.
4. Average number of drugs prescribed by generic name was 93.90% (185 out of 197).
5. Average number of drugs prescribed from National List of Essential Medicines (NLEM-2015) was 70.55%.

Details of breakthrough seizures were given by informant/LAR's recall of particular event. In 1st monthly follow-up, 26 patients (49.05%) had experienced breakthrough seizures of at least one episode. Number of patients with breakthrough seizures was in decreasing trend during second and third follow-ups (10, 21.73%, and 3, 10.33%) (Table 4). Out of these 26 patients who had breakthrough seizures in first follow-up, 18 patients were on monotherapy, whereas four patients were on dual

therapy and four patients on poly therapy. Out of these 26 patients, number of patients experienced breakthrough seizures in 2nd and 3rd follow-ups were 9/10 and 3/3.

Out of 27 patients who had history of low birth weight (LBW) < 2.51 kg, 13 (48.14%) patients had experienced breakthrough seizures of at least one episode in first follow-up and one patient suffered breakthrough seizures in both second and third follow-ups. Out of 13 patients with positive family history, 6 (46.15%) patients had breakthrough seizures during first follow-up, 5 (38.46%) patients had breakthrough seizures in second follow-up, and 1 (7.69%) patient in third follow-up (Tables 5 and 6).

A total of seven out of 26 patients (who had breakthrough seizures) in 1st follow-up required change in treatment, whereas four out of ten patients (who had breakthrough seizures) in 2nd follow-up and one out of three patients (who had breakthrough seizures) in 3rd follow-up required change in treatment (Tables 7 and 8).

Adherence is the degree to which patients' treatment-related behaviors (e.g., taking medication, keeping follow-up medical appointments, and changing dietary habits) are consistent with instructions or recommendations provided by health professionals. Average days of refill interval of patients during monthly follow-up were 27.49 ± 7.64, 30.21 ± 11.86, and 28.27 ± 2.86 days (mean ± SD) in 1st, 2nd, and 3rd follow-ups. Number of patients missed to take AEDs were 5, 6, and 2 in 1st, 2nd, and 3rd follow-ups, respectively.

Treatment adherence 95% was high in the 3rd follow-up (96%) compared to the 1st follow-up (78.72%). As adherence improved, the break-through seizures were decreased (49.05% vs. 10.33%); however, the association was not statistically significant (p=0.25, Fisher's exact test). There is a significant correlation between breakthrough seizures and non-compliance with a score of R=0.4767 on the Pearson correlation coefficient and rates of probability values being p<0.05.

Table 2: Prescribed AEDs according to the type of epilepsy in pediatric epilepsy patients (n=73)

Sr. No.	Type of epilepsy	Prescribed antiepileptic drug
1	GTCS/GTC epilepsy	Sodium valproate (24), levetiracetam (7), carbamazepine (4), clobazam (2), clonazepam (1), oxcarbazepine (1), and phenobarbitone (1)
2	Remote symptomatic epilepsy (RSE)	Sodium valproate (9), levetiracetam (4), carbamazepine (3), and topiramate (1)
3	Focal epilepsy	Carbamazepine (3), levetiracetam (3), sodium valproate (2), and clobazam (1)
4	Complex febrile convulsion	Sodium valproate (3)
5	Unprovoked seizures	Sodium valproate (1), and carbamazepine (1)
6	Childhood absence epilepsy	Sodium valproate (1)
7	Partial epilepsy	Sodium valproate (1)

Table 3: Analysis of mean dose of prescribed AEDs in pediatric epilepsy patients

Prescribed antiepileptic drug	Mean dose in mg/kg/day
Sodium valproate	19.25
Levetiracetam	22.7
Carbamazepine	14.4
Clobazam	4.22
Clonazepam	0.03
Oxcarbazepine	10
Phenobarbitone	6
Topiramate	2

Rationality assessment of AED prescriptions

Our study was designed to analyze the prescribing pattern and rationality in prescriptions according to national and international standard treatment guidelines in a tertiary care teaching hospital in India. We have compared the rationality with the ILAE (International League Against Epilepsy) guideline 2017, NICE (National Institute for Health and Care Excellence) guideline (updated in 2020), and recent IAP (Indian Association of Pediatrics) guidelines. Rationality was assessed for selection of drug and selection of the right dose.

Out of 53 prescriptions of pediatric epilepsy patients, 37 prescriptions (where AED as monotherapy was prescribed) were analyzed for rationality assessment. According to the global standard ILAE guideline, 29.72% of prescriptions were found to be irrational and 70.28% of prescriptions were rational. Similarly, according to the NICE guideline of the United Kingdom, 78.73% of prescriptions were found rational and 21.67% prescriptions were irrational, whereas according to recent IAP guidelines 43.24% prescriptions were irrational and 56.76% prescriptions were rational (Fig. 2). Analysis of irrational prescription assessment according to IAP guidelines is given in Table 14. According to IAP guidelines, six prescriptions were having inappropriate selection of AED which was not recommended for specific type of epilepsy. Whereas in five prescriptions, starting dose was higher than the recommended dose range of selected AEDs.

DISCUSSION

This prospective, observational, and single-center study was carried out in the department of Pediatrics at Civil hospital, Ahmedabad in Gujarat. A total of 53 pediatric patients attending the pediatric epilepsy outdoor clinic were included in the study. Majority of the patients were in the age group of 7 to 9 years, which is similar to study done by Bhatt *et al.* conducted at Gujarat in pediatric neurology

Table 4: Analysis of breakthrough seizures in pediatric epilepsy patients at follow-ups

Characteristics	First follow-up (n=51) (%)	Second follow-up (n=46)	Third follow-up (n=29)
Number of patients experienced breakthrough seizures (%)	26 (49.05)	10 (21.73)	3 (10.33)
Average time (minutes) (mean±S.D.)	3.2±1.19 min	2.7±1.05 min	3.66±1.15 min
Average number of episodes (mean±S.D.)	2.68±2.27	1.9±1.08	1.6±1.15
History of missed AED dose (number of patients)	4	2	0
Dose adjustment/change in AED in next follow-up (number of patients)	7	4	1

Table 5: AEDs combinations in pediatric epilepsy patients (n=16)

Dual therapy (combination of two AEDs)	Number of patients (n=12)	Polytherapy (combination of >2 AEDs)	No. of patients (n=4)
Sodium valproate+Levetiracetam	4	Sodium valproate+Levetiracetam+Carbamazepine	2
Levetiracetam+Clobazam	2		
Sodium valproate+Carbamazepine	1		
Carbamazepine+Levetiracetam	1	Sodium valproate+Levetiracetam+Clobazam	1
Sodium valproate+Clobazam	1		
Levetiracetam+Clonazepam	1		
Sodium valproate+Oxcarbazepine	1	Sodium valproate+Carbamazepine+Clobazam	1
Sodium valproate+Phenobarbitone	1		

Table 6: Evaluation of predisposing factors for breakthrough seizures in pediatric epilepsy patients (n=53)

Characteristics	Breakthrough seizures in number of patients		p-value
	Yes	No	
H/O low birth weight			
Yes	21	6	p=0.00*
No	5	21	
H/O NICU admission			
Yes	9	3	p=0.04*
No	17	24	
Positive family history			
Yes	6	7	p=0.80
No	20	20	
EEG abnormality			
Yes	16	22	p=0.10
No/Not done	10	5	
AED prescribed as			
Monotherapy	18	19	p=0.92
Polytherapy	8	8	
Conventional AED			
Newer AED	15	18	p=0.77
Both	2	2	
(Conventional AED+Newer AED)	9	7	
Compliant	16	22	p=0.10
Non-compliant	10	5	

*Chi-square test was used to determine significant factors associated with breakthrough seizures and p value ≤ 0.05 was considered to be statistically significant.

OPD [10]. A discrepancy in the mean age and age group in the above-mentioned studies might be due to differences in the sample size. Male:female ratio was 1.3:1 in our study. Similar results were also found out in a study done by Panda *et al.* conducted at Pune, Maharashtra, and Hasan *et al.* conducted in Malaysia [11,12]. The reason might be the sex ratio of the study population of different studies is also showing male preponderance.

The most common clinical presentation of patients in was the history of convulsion recently associated with either tongue bite, frothing from the mouth and/or body movement involvement, urinary incontinence, etc. A study done by Garfinkle *et al.* mentioned that

70.96% of patients were having global developmental delay after neonatal seizures [13].

Out of 53 patients, 5 (9.43%) patients were born preterm and 11(20.75%) patients were having history of lower segment cesarean section (LSCS), whereas 12 (22.65%) patients were having history of admission in neonatal ICU after birth. Study done by Crump *et al.* showed that there is strong association between preterm birth and epilepsy (odds ratio [OR] for epilepsy in preterm babies was 4.98) [14]. Average weaning age of 86.79% patients was 18 ± 4.19 months. About 26.41% patients received breast feeding after 2 h in our study.

Positive family history was present in 24.52% patients. Parental consanguinity was present in 5.66% patients. Study done by Lekshmi *et al.* at Kerala showed that only 15.2% patients had a family history of seizures [15]. Difference in the results of our study with other studies might be due to different study populations as well as heterogeneous group of genes and environmental factors contributing to the pathogenesis of epilepsy.

Most of the patients presented to the pediatric epilepsy outdoor patient department with a history of seizures with symptoms of developmental delay (35.84%), hyperactivity (16.30%), and involuntary movements (14.30%). EEG was the most commonly used investigation for diagnosing different type of epilepsy. In the present study, 64.50% of patients were having abnormal EEG, whereas CT scan and MRI scan were abnormal in 5.66% and 15.09% of patients, respectively.

Most common diagnosis of the patients in pediatric epilepsy clinic was generalized tonic-clonic seizure (GTCS) and GTC epilepsy followed by remote symptomatic epilepsy (RSE). However, a study done by Bhatt *et al.* at Gujarat showed partial seizure being most common type of epilepsy followed by generalized tonicclonic seizure (GTCS), while study done by Panda *et al.* conducted at Maharashtra found GTCS was the most common form of seizure [10,11]. The reason for discrepancy might be difference in disease prevalence in different countries as well as in states of India.

The commonly prescribed AEDs in pediatric epilepsy patients was sodium valproate 77.36% followed by levetiracetam 26.42% and carbamazepine 20.75%. A study conducted at Singapore showed that sodium valproate was the most frequently prescribed AED (36.8%), followed by carbamazepine (30.2%) and lamotrigine (10.4%) [12]. About 69.81% of patients received AED as monotherapy and 30.19%

Table 7: Change in treatment in breakthrough seizures patients in follow-ups

Primarily prescribed AED	Type of change in treatment	Changed/added AED	Number of patients	Mean Dose in mg/kg/day
Sodium valproate	Dose increased	Sodium valproate	1	Increased from 25 to 35
Levetiracetam (1), carbamazepine (1)	Changed primary AED	Sodium valproate	2	17.5
Levetiracetam (2), carbamazepin (2)	Added to regimen	Sodium valproate	4	20
Sodium valproate (2), carbamazepine (1)	Added to regimen	Levetiracetam	3	13.5
Sodium valproate (2), levetiracetam (2)	Added to regimen	carbamazepine	4	15.5
levetiracetam (2), carbamazepine (1)	Added to regimen	Clonazepam	3	0.03

Number of patients AED dose changes=1, Number of patients with primary AED change=2, Number of patients in which AED added=9, Number of patients in which one AED added=4, Number of patients in which two AEDs added=5, Total number of patients with treatment changed=12

Table 8: Characteristics of compliant and non-compliant pediatric epilepsy patients

Variables	Compliant patients (n=38)	Non-compliant patients (n=15)
Age (mean)	6.58±3.42 years	7.4±2.29 years
Gender		
Male	21	9
Female	17	6
Residence		
Urban	32	13
Rural	6	2
Family history	8	5
Positive family history+Parental consanguinity +	3	0
H/O Low birth weight +	21	6
H/O NICU admission	9	3
Abnormal investigations		
EEG	27	7
CT scan	1	2
MRI scan	5	3
AED prescribed on visit as		
Monotherapy	29	8
Dual therapy	6	6
Polytherapy	3	1
Conventional AED	26	7
Newer AED	3	1
Conventional AED+Newer AED	9	7
Number of patients with breakthrough seizure	16 (42.10%)	10 (66.67%)
Number of patients required change in treatment in follow-ups	8 (21.05%)	4 (26.67%)

of patients received AEDs as polytherapy. Polytherapy was prescribed in hemiplegic cerebral palsy and spastic cerebral palsy with global developmental delay, generalized seizures with mental retardation and blindness, neurofibromatosis-1, and tuberous sclerosis.

The most commonly prescribed AED combinations on were sodium valproate + levetiracetam (7.54%), sodium valproate + levetiracetam + carbamazepine (5.77%), levetiracetam + clobazam (5.77%), etc. This is in contrast to a study done by Tan *et al.* at Singapore that observed sodium valproate + carbamazepine as most common combination therapy prescribed [16].

Conventional AEDs were still prescribed more compared to newer AEDs and combination of both. Similar findings were noted in study conducted at Karnataka that AED as monotherapy prescribed in 62.12% and polytherapy in 37.87% of patients [17].

Percentage of drugs prescribed by generic name was very high in our study as compared to other studies [18,19]. In the present study,

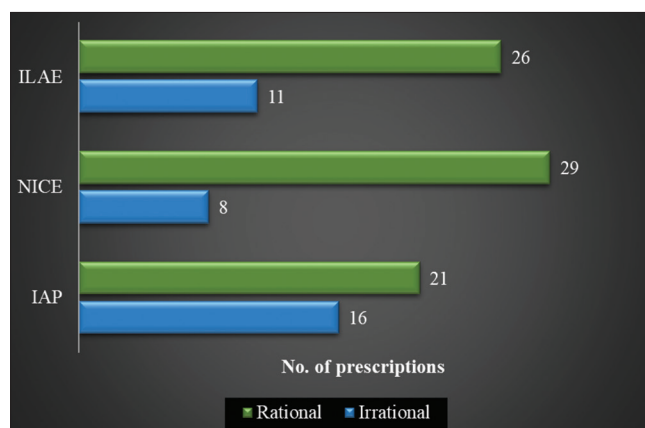


Fig. 2: Rationality assessment of AEDs prescriptions according toretic guidelines (n=37). *ILAE: International league against epilepsy, NICE: National Institute for Health and Care Excellence, IAP: Indian Association of Pediatrics

84.93% of the AEDs were prescribed twice a day which is similar to study done by May *et al.* conducted at Germany [20].

In our study, there is attrition in the third follow-up as major reason could be the COVID-19 pandemic crisis in year 2020 during our study period. Results of our study regarding breakthrough seizures were similar with the study done by Panda *et al.* [21], whereas breakthrough seizures were higher in other studies done by Kaddumukasa *et al.* and Al-Kattan *et al.* [22,23] Discrepancy with the results with Indian studies and other studies might be due to different study population as other studies were in adult population as well as the repeated dose adjustments according to weight in pediatric patients. Poor compliance associated with taking multiple doses of AEDs daily for longer duration might also be the reason for it. Previously done study by Kaddumukasa *et al.* conducted at Uganda also agreed with missed AED represented most frequent precipitating factor, accounting for 46.6% of breakthrough seizures [24].

For analysis of association of different factors with breakthrough seizures, Chi-square test was used. Low birth weight and NICU admission after birth were found to be significantly associated with breakthrough seizures ($p < 0.05$), while positive family history, EEG abnormality, type of AED therapy, and patients' compliance were not found to be significantly associated with breakthrough seizures ($p > 0.05$). There is a significant correlation between breakthrough seizures and non-compliance with a score of $R = 0.4767$ on the Pearson correlation coefficient (p -value < 0.05). As adherence improved, the break-through seizures were decreased (49.05% vs 10.33%) However, the association was not statistically significant ($p = 0.25$, Fisher's exact test). Results from our study and other studies showed that non-adherence to the prescribed treatment may be one of the most important cause of poorly controlled epilepsy [24,25].

Change in treatment was required in 12 patients during follow-ups mainly to achieve better seizure control. In one patient AED dose

changed, in two patients primary AED changed, in nine patients AED added, four patients in which one AED added, five patients, in which two AEDs added, total number of patients, in which treatment changed = 12. Carbamazepine, levetiracetam, and clonazepam were common AEDs used as add-on AEDs. A recent study showed 60% patients required increase in the dose of prescribed AED, whereas 17% patients required the addition of AED [23].

In our study, majority of prescriptions were according to NICE guideline, which is similar to the study conducted at Karnataka [26]. Levetiracetam is recommended only as add-on therapy in IAP guidelines, whereas it is recommended as first line in NICE guideline. In our study, oxcarbazepine and topiramate were prescribed in lower dose compared to recommended, whereas clobazam was given in higher dose. Difference in type specific AEDs and dose recommendations is the main reason for the difference in the rationality among various guidelines.

Like other studies, our study also has several limitations. It was single-center study and sample size was less. Hence, the findings cannot be generalized to overall pediatric epilepsy population. Those patients who had uncontrolled seizures despite change in treatment were not followed-up after 3 months as per the study protocol. Serum levels (therapeutic drug monitoring) of prescribed drugs were also not measured. No ADRs observed during our study period attributed to short follow-up period and lost to follow-up during COVID-19 pandemic. We could not measure long term medication adherence, cost of the drug treatment, and improvement in scholastic performance as well as quality of life of patients.

Despite above limitations and COVID-19 pandemic during our study period, we were able to follow-up decent number of patients till 3 months. We have assessed rationality of prescribed AEDs according to various treatment guidelines such as NICE, ILAE, and IAP guidelines. We have analyzed breakthrough seizures and its association with low birth weight, NICU admission, family history, prescribed therapy, and compliance of patients.

CONCLUSION

Through our study, it was concluded that conventional AEDs, that is, sodium valproate and carbamazepine are still commonly used first-line drugs for pediatric epilepsy patients. However, newer AEDs (e.g., levetiracetam) are frequently prescribed as primary AED and adjunct therapy. In our hospital, majority of AEDs were prescribed according to NICE guideline and by generic name. Low birth weight and NICU admission associated with breakthrough seizures. We found significant correlation between breakthrough seizures and non-compliance. This study highlights the need of prescribing pattern studies of AEDs in pediatric patients, so that lacunae in system can be identified and strategies can be rectified.

AUTHORS CONTRIBUTIONS

All the authors contributed to protocol planning and designing. Dr. KaushalPanchal collected the data. All the authors contributed to data analysis and manuscript preparation.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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None.

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