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### Adverse drug reactions of antiepileptic agents among pediatric patients at tertiary care teaching hospital of Gujarat- a cross-sectional study

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#### ABSTRACT

##### Background and Aim

Epilepsy is one of the most common neurological disorders characterized by recurrent episodic paroxysmal involuntary clinical events associated with abnormal electrical activity from the neurons. Antiepileptic treatment in pediatric age group should be aimed to control seizures associated with the lowest possible occurrence of adverse effects, thus allowing the child to become an active member of the community. Present study was performed with an aim to evaluate the adverse drug reactions (ADRs) caused by the anti-epileptic drugs Among Pediatric Patients of tertiary care teaching hospital of Gujarat.

##### Material and Methods

The present cross-sectional study was conducted at the epilepsy clinic of Department of Paediatrics, Tertiary Care teaching hospital of Gujarat, on patients diagnosed to have epilepsy July 2014 to October 2014. Hundred Paediatric patients of either gender diagnosed to had epilepsy and taking treatment from pediatric epilepsy clinic OPD, Tertiary Care teaching hospital of Gujarat. Patient's detailed medical history, drug reports, demographic data, type of seizures, the anti-epileptic drugs prescribed and the adverse drug reactions (ADRs) reported by the patients were recorded in a pre-structured data entry form.

##### Results

Out of 100. GTCS was found to be the most common (55%) form of epilepsy among pediatric patients and Carbamazepine was the most commonly prescribed (41%) AED followed by sodium valproate (38%). 24 patients suffered from ADRs of antiepileptic drugs. Out of which 7 patients suffered from drowsiness and suspected drug for this ADR were clobazam, levetiracetam and carbamazepine. Six patients suffered from irritability and suspected drugs for this ADR were clobazam, carbamazepine.

##### Conclusion

Total 24 patients suffered from ADRs of antiepileptic drugs. Drowsiness was most commonly observed ADR and suspected drugs for this ADR were clobazam, levetiracetam and carbamazepine.

**Keywords:** Adverse drug reactions, Carbamazepine, Drowsiness, Epilepsy

## INTRODUCTION

Epilepsy is one of the most common neurological disorders characterized by recurrent episodic paroxysmal involuntary clinical events associated with abnormal electrical activity from the neurons. [1] The term *seizure* refers to a transient alteration of behaviour due to the disordered, synchronous and rhythmic firing of populations of brain neurons. Seizures can be "non-epileptic" when evoked in a normal brain by treatments such as electroshock or chemical convulsants or "epileptic" when occurring without evident provocation. [2]

Epilepsy affects about 20-40 million people worldwide. [7] It is the second most common neurological disorder, after stroke. [3] The rates are similar between different ethnic groups and slightly higher for men compared to women. Higher rates are reported in underdeveloped countries and lower socioeconomic classes. Across age groups, there is a bimodal distribution with higher incidence at extremes of age. [4]

Epilepsy is the most common neurological disorder in children with an incidence of about 8 per 1000 children under the age of seven years. [3] This childhood epilepsy remains a challenge to treat. Despite the increase in the number of Antiepileptic 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 every year, and of those, 30,000 will develop epilepsy. [5]

A large number of drugs are currently available for the treatment of epilepsy. Older/conventional drugs like Phenytoin, Carbamazepine, Valproic acid and Ethosuximide are commonly used as first line drugs. They are relatively less expensive than the newer antiepileptic drugs like Gabapentin, Lamotrigine, Vigabatrin, Topiramate, Tiagabine and Zonisamide are the newer ones and currently used as add-on or alternative therapy.

Antiepileptic treatment in paediatric age group should be aimed to control seizures associated with the lowest possible occurrence of adverse effects, thus allowing the child to become an active member of the community.

Amongst the various factors affecting anti-epileptic drug (AED) usage, the major determinants are types of epilepsy, age and gender of patient, ease of dosing, efficacy, long term side effect profile, neuropsychiatric profile, sedative burden and interaction with other medications, co-morbid conditions medicines, affordability of the patient and preference of the treating physician as well as the practice setting.

With above facts, present study was performed with an aim to evaluate the adverse drug reactions (ADRs) caused by the anti-epileptic drugs Among Pediatric Patients of Tertiary Care teaching hospital of Gujarat.

## MATERIALS AND METHOD

The present cross-sectional study was conducted at the epilepsy clinic of Department of Paediatrics, Tertiary Care teaching hospital of Gujarat, on patients diagnosed to have epilepsy July 2014 to October 2014. Hundred Paediatric patients of either gender diagnosed to had epilepsy and taking treatment from pediatric epilepsy clinic OPD, Tertiary Care teaching hospital of Gujarat. Based on a previous record, on an average 14-15 paediatric patients came to epilepsy clinic per week. Amongst them 5-6 were new patients while remaining came for follow-up. On this basis of estimated sample size of patients who had received at least 2 months antiepileptic drug therapy was calculated as 100.

Inclusion Criteria were: Patients of both gender and age less than 18 years, diagnosed to have epilepsy, and receiving drug therapy for at least 2 months were included in our study.

Exclusion criteria were: Patients with secondary epilepsy due to head injury, cerebral palsy, stroke, metabolic disorders etc, Patients not willing to participate in the study were excluded from our study.

Patients fulfilling the inclusion and exclusion criteria were included in the study. Patient / Legally Authorized Representative (LAR) were informed about the nature of study. Written informed consent was obtained from parent and ascent was obtained from child whenever applicable and only those patients from whom informed consent was obtained were enrolled in the study. Patient's detailed medical history, drug reports, demographic data, type of seizures, the anti-epileptic drugs prescribed and the

adverse drug reactions (ADRs) reported by the patients were recorded in a prestructured data entry form.

## STATISTICAL ANALYSIS

The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 15 (SPSS Inc. Chicago, IL, USA) Windows software program. The variables were assessed for normality using the Kolmogorov-Smirnov test. Descriptive statistics were calculated. Data was presented as either Percentage or Mean  $\pm$  SD.

## RESULTS

Total 100 pediatric patients of either gender diagnosed to had epilepsy and who had received at least 2 months antiepileptic drug therapy from pediatric epilepsy clinic OPD, Tertiary Care teaching hospital of Gujarat during July 2014 to October 2014 were recruited in the study.

As shown in table 1, among 100 patients recruited, 40 patients each belonged to 5-10 and 10-15 year age group while 17 patients were from 0 – 5 year age group and remaining 3 patients were from 15-18 year age group, at the time of admission. Out of 100 patients, 63 were males; while 37 were females. (Table 2)

**Table 1: Age Wise Distribution**

| Age                         | No of Patients |
|-----------------------------|----------------|
| 0-5 year (Age)              | 17             |
| 5-10 year (Age)             | 40             |
| 10 – 15 year (Age)          | 40             |
| 15 – 18 year (Age)          | 3              |
| <b>Total No of Patients</b> | <b>100</b>     |

Out of 100, almost half (47%) of sample population had family income <50000 INR annually while 34% had annual family income of 50000 – 100000 INR. Out of 100 patients 72 patients were

school going and 28 patients had never gone school. Out of 100 patients 87 patients were immunized and remaining 13 patients were partial / non immunized.

**Table 2: Gender wise distribution**

| Gender       | Total No of Patients (100) |
|--------------|----------------------------|
| Male         | 63                         |
| Female       | 37                         |
| <b>Total</b> | <b>100</b>                 |

Out of 100 patients 79 Patients were underweight, 20 were classified into normal weight category while only 1 child was overweight (obese class – 1). (Table – 20, Figure 10-A, Figure 7-A,B,C) Out of 100 patients 91 patients had no family history of epilepsy while remaining 9 patients had family history of epilepsy.

Out of 100 patients EEG alone was used as a diagnostic test in 49 patients and EEG and CT SCAN were used as a diagnostic test in 35 patients. EEG and

MRI were used as diagnostic tests in 9 patients and in remaining 7 patients EEG, MRI, and CT SCAN all were used as diagnostic tests. Out of 100 patients 55 % patients had generalized tonic clonic seizure while 18 and 19 % patients had Partial seizure and focal seizure respectively. Myoclonic seizure and benign rolandic seizure were seen in 5 and 2 patients respectively. Only 1 patient suffered from absence seizure. (Table 3)

**Table 3: - Distribution of Patients According To Type of Seizure**

| GTCS | Focal Seizure | Partial Seizure | Myoclonic Seizure | Benign Rolandic Epilepsy | Absence Seizure | Total No of Patients |
|------|---------------|-----------------|-------------------|--------------------------|-----------------|----------------------|
| 55   | 19            | 18              | 5                 | 2                        | 1               | 100                  |

Out of 100 patients, 53 patients had 3 -5 episodes per month while 41 patients were had 1- 2 episodes per month. 4 patients were having 6 – 8 episodes of

seizure per month while 2 patients had suffered from >8 episodes of seizure per month before AED therapy.

**Table 4: No of Seizure Episode per Month before Antiepileptic Drug Therapy**

| 1 – 2 Episodes of Seizure Per Month | 3– 5 Episodes of Seizure Per Month | 6 – 8 Episodes of Seizure Per Month | > 8 Episodes of Seizure Per Month | Total No. of Patients |
|-------------------------------------|------------------------------------|-------------------------------------|-----------------------------------|-----------------------|
| 41                                  | 53                                 | 4                                   | 2                                 | 100                   |

Out of 100 patients, 63 patients were seizure free while 35 patients had 1- 2 episodes per month after starting AED therapy. 2 patients were having 3 – 4 episodes of seizure per month after AED therapy.

In majority of patients significant decrease in no. of seizure episode (P<0.0001) was observed after starting AED.

**Table 5: No of Seizure Episode per Month after Antiepileptic Drug Therapy**

| Seizure Free Patients | 1 - 2 Episodes of Seizure Per Month | 3 – 4 Episodes of Seizure Per Month | Total No. of Patients |
|-----------------------|-------------------------------------|-------------------------------------|-----------------------|
| 63                    | 35                                  | 2                                   | 100                   |

**Table 6: Adverse Drug Reactions (Adrs) Observed In Patients of Pediatric Epilepsy**

| Adverse drug reactions | No of patients | Suspected Drugs                       |
|------------------------|----------------|---------------------------------------|
| Drowsiness             | 7              | Clobazam ,Levetiracetam Carbamazepine |
| Irritability           | 6              | Clobazam , Carbamazepine              |
| Anorexia               | 5              | Sodium Valproate                      |
| Headache               | 3              | Carbamazepine                         |
| Vomiting               | 1              | Carbamazepine                         |
| Vertigo                | 1              | Carbamazepine                         |
| Nausea                 | 1              | Carbamazepine                         |

As per the table 6 total 24 patients suffered from ADRs of antiepileptic drugs. Out of which 7 patients suffered from drowsiness and suspected drug for this ADR were clobazam, levetiracetam and carbamazepine. Six patients suffered from irritability and suspected drug for this ADR were clobazam,

carbamazepine. 5 patients suffered from anorexia and suspected drug for this ADR was sodium valproate. 3 patients suffered from headache and suspected drug for this ADR were carbamazepine and remaining 2 patients suffered from vomiting and vertigo and suspected drug for this ADRs was carbamazepine.

**Table 7: Distributions of Adverse Drug Reactions as Per Various Causality Assessment Scales**

| Adverse Drug Reactions | No of Patients | Causality Assessment By WHO (UMC) Criteria <sup>83</sup> | Hartwig and Siegel Severity Assessment Scale <sup>85</sup> | Schumock and Thornton Preventability Scale. <sup>86</sup> | Causality Assessment By Naranjo Scale <sup>84</sup> |
|------------------------|----------------|--|--|---|---|
| Drowsiness             | 7              | Possible   | Mild   | Definitely Preventable                                    | Possible  |
| Irritability           | 6              | Possible   | Mild   | Definitely Preventable                                    | Possible  |
| Anorexia               | 5              | Possible   | Mild   | Definitely Preventable                                    | Possible  |

|          |   |          |      |                        |          |
|----------|---|----------|------|------------------------|----------|
| Headache | 3 | Possible | Mild | Definitely Preventable | Possible |
| Vomiting | 1 | Possible | Mild | Definitely Preventable | Possible |
| Vertigo  | 1 | Possible | Mild | Definitely Preventable | Possible |
| Nausea   | 1 | Possible | Mild | Definitely Preventable | Possible |

As per the table 7 we can observe that as per WHO (UMC) 83 and Naranjo causality assessment scale<sup>84</sup> all ADRs fell into possible category and as per Hartwig and siegel severity assessment scale<sup>85</sup>

all ADRs were mild. As per Schumock and Thornton preventability scale<sup>86</sup> all ADRs were defiantly preventable.

**Table 8: Concomitant Medications**

| Concomitant Medications                                   | Prescribed in No of Patients | Reasons For Prescribing     |
|---|------------------------------|-----------------------------|
| <b>Amoxicillin Plus Potassium Clavulanate Combination</b> | 2                            | Cold & Fever                |
| <b>Paracetamol</b>  | 4                            | Fever                       |
| <b>Risperidone</b>  | 3                            | Behaviour Disturbances      |
| <b>Chlorpheniramine</b>                                   | 4                            | Cold , Fever                |
| <b>Multivitamin Syrup</b>                                 | 2                            | As a Nutritional Supplement |
| <b>Cotrimoxazole</b>                                      | 1                            | Cold & Fever                |
| <b>MVBC</b>   | 20                           | As a Nutritional Supplement |
| <b>Folic Acid</b>   | 18                           | As a Nutritional Supplement |
| <b>Calcium Tablets</b>                                    | 11                           | As a Nutritional Supplement |
| <b>Lorazepam</b>  | 1                            | Behaviour Disturbances      |
| <b>Benzhexol</b>  | 1                            | Behaviour disturbances      |
| <b>Chlorpromazine</b>                                     | 1                            | Behaviour disturbances      |
| <b>Insulin</b>  | 1                            | Diabetes                    |
| <b>Budesonide</b>   | 1                            | Asthma                      |
| <b>Salbutamol</b>   | 1                            | Asthma                      |

As per table 8 we can observe that MVBC was the most commonly prescribed concomitant drug (20 patients) followed by folic acid and calcium in 18 & 11 patients respectively. PCM and chlorpheniramine was prescribed in 4 patients who were suffering from fever and cold. Risperidone was prescribed in 3 patients who were suffering from behavior disturbances. Amoxicillin plus potassium clavulanate combination was prescribed in 2 patients who were suffering from cold and fever. Multivitamins syrup was prescribed in 2 patients as a nutritional supplement. Cotrimoxazole was prescribed in 1 patient who was suffering from cold and fever. Lorazepam, benzhexol, chlorpromazine were prescribed in 1 patient who was suffering from

behavior disturbances. Insulin was prescribed in 1 diabetic patient. Budesonide and salbutamol were prescribed in 1 patient with asthma.

## DISCUSSION

Epilepsy is the most common neurological disorder in children characterized by spontaneous propensity for recurrent and unprovoked seizures and it remains a Challenge to treat. [7, 8] Despite of overall increase in number of antiepileptic drugs, more than 25% of children with childhood epilepsy continue to have seizures. [9]

The overall aim of antiepileptic treatment should be to control seizures with the lowest possible

occurrence of adverse effects, allowing the child to become an active member of the community.

In our study, majority of the patients (40 %) belonged to age group 6 to 10 years with a Mean age of patient was found to be  $9.14 \pm 3.65$  years. This is in consonance with the study carried out in Malaysia. [10] and it is in contrast to the some other study in which majority of children fall in 0 to 3 year age group. [11]

In the present study, out of total, 86% patients were immunized, which is almost similar to study carried out by Mistry et al. [12] Certain diseases like measles, diphtheria, pertussis, tetanus etc., cause brain damage as well as febrile episodes which may result in febrile convulsions. So immunization plays an important role in prevention of epilepsy.[13]

Majorities of the patients (72 %) included in our study were going to school. Due to frequent seizure episodes, maintenance of regular activity may become difficult for the patients who may result in school dropout or irregularity in school.

In our study, EEG was used in all 100 patients for diagnosis of epilepsy which was higher as compared to previous study conducted by Mistry et al.[12] EEG alone was used as an investigation of epilepsy in 49% patients. As per American academy of neurology guideline for epilepsy, EEG plays only a part of routine neurodiagnostic evaluation for diagnosis of epilepsy and on the basis of normal and abnormal EEG alone, we can't confirm the diagnosis of epilepsy.[13] In our study we found that MRI and CT Scan was done in only 16% and 42% patients respectively.

The probable reason, why the investigations were not carried out as per American academy of neurology guidelines is, as majority of the patients belonged to lower socioeconomic class and almost 81% patient's family had their annual income below 100000 INR/Year, they may not afford the cost of CT Scan and MRI.

Generalized tonic clonic seizure was the most commonly observed seizure in the present study. Percentage of patients suffering from generalized tonic clonic seizure was higher than that observed by other studies.[12, 14] The most commonly prescribed drug in the present study was carbamazepine followed by sodium valproate which is similar to study conducted by Mistry et al. [12] and in contrast to study conducted by Kousalya K et al[11] which

reports that sodium valproate was the commonest drug used for seizure, followed by phenytoin.

In our study we found that the most commonly prescribed drug in GTCS was Sodium valproate which was similar to studies conducted by Mistry et al [12] and Kousalya K et al [11]. While most commonly prescribed drug in Focal Seizure was Carbamazepine which was similar to studies conducted by Mistry et al[12] and in contrast to study conducted by Kousalya K et al[11] which reports that phenytoin was the commonest drug used for focal seizure.

As per the guidelines of treatment of epilepsy sodium valproate and Carbamazepine are recommended for GTCS Patients and focal seizure patients respectively.[15, 16] In our study we found that most commonly prescribed newer drug was clobazam this is in consonance with study carried out by Mistry et al. [12]

Total 24 adverse drug reactions were observed in the present study. In our study, we found that most common ADR was drowsiness (7 patients) followed by irritability and most the common drug involved in ADR was carbamazepine followed by clobazam whereas in a study conducted by Mistry et al. [12], irritability was most common ADR and sodium valproate and carbamazepine were the most common drugs responsible for ADRs. All ADRs found in our study fall into possible category as per WHO causality assessment scale, and were found mild as per Hartwig & Siegel severity assessment scale.

## CONCLUSION

In the present study, GTCS was the most commonly observed type of seizure and Carbamazepine was the most frequently prescribed drug followed by sodium valproate. Total 24 patients suffered from ADRs of antiepileptic drugs. Drowsiness was most commonly observed ADR and suspected drug for this ADR were clobazam, levetiracetam and carbamazepine. As per WHO (UMC) and Naranjo causality assessment scale all ADRs fell into possible category and as per Hartwig and siegel severity assessment scale all ADRs were mild. As per Schumock and Thornton preventability scale all ADRs were definitely preventable.

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