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Research Article**Drug utilization pattern of antiseizure drugs and their adverse effects in the pediatric population, in a tertiary care hospital attached to a medical college****Rusva A. Mistry^{1*}, Krunal C. Solanki¹, Hiren K. Prajapati¹, Tejas M. Doshi², Hiren R. Trivedi¹**¹Department of Pharmacology, M. P. Shah Medical College, Jamnagar, Gujarat, India,²Department of Medicine, Guru Gobind Government Hospital, Jamnagar, Gujarat, India**Received:** 23 January 2014**Accepted:** 02 February 2014***Correspondence to:**Dr. Rusva A. Mistry,
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ABSTRACT

Background: Epilepsy is “a condition characterized by recurrent (two or more) seizure, unprovoked by any immediate identified cause.” The desired outcome of antiseizure drug (ASD) therapy is to be seizure-free throughout the rest of life. The objective was to study the utilization pattern and adverse drug reactions (ADRs) associated with the use of ASDs in pediatric outpatients in epilepsy clinic.

Methods: This cross-sectional, observational and single center study was carried out over a period of 1 year in 430 pediatric patients. Analyzed data included demographic details and drugs prescribed in respective seizure types along with ADRs due to ASDs.

Results: In a total 430 patients analyzed, seizure were most commonly observed in boys (69.8%) in 6-10 year of age (45.3%), with a positive family history in (16%), with no specific cause of seizure in (71.6%), with most common type was focal seizure in (62.3%), which was mainly treated with carbamazepine (73.8%). Most common ADR was irritability (32.2%) with Valproate being main drug. 87.3% ADRs were in “possible” as per World Health Organization causality assessment scale, 94.9% ADRs were “mild” as per Hartwig and Siegel severity assessment scale and 98.3% ADRs were “preventable” as per Schumock and Thornton preventability scale.

Conclusion: Focal seizure was most common type of seizure observed mainly in boys of 6-10 year with carbamazepine as mainly prescribed drug. Use of appropriate ASDs in the majority of patients as per guidelines, has decreased number of ADRs in our study. Prescribing drugs were mainly from essential drug list and by generic names.

Keywords: Epilepsy, Drug utilization pattern, Adverse drug reaction

INTRODUCTION

Epilepsy is the most common neurological disorder in children. A seizure (“to take possession of”: From the Latin *sacire*) is paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy describes a condition in which a person has recurrent (two or more) unprovoked seizures due to a chronic, underlying process. About 5-10% of the population may have at least one seizure, with the highest incidence occurring in early childhood and late adulthood.¹ Epilepsy, especially childhood epilepsy, remains a challenge to treat. Despite the increase in the number of antiseizure drugs (ASDs), more than 25% of children with childhood epilepsy continue to have seizure.²

Pharmacoepidemiology is the study of use and effects/side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective

use of drugs in the population thereby improving health outcomes. Drug utilization study (DUS) is an essential part of pharmacoepidemiology and is defined as “the marketing, distribution, prescription, and use of drugs in society, with specific emphasis on the resulting medical, social & economic consequences.”³ Adverse effects are highly prevalent in the drug treatment of epilepsy. Polytherapy is a common practice for the management of epilepsy despite of a significant increase in side-effects.⁴

Our hospital is a tertiary care hospital attached to a medical college. Every Wednesday between 4 pm and 6 pm “epilepsy clinic” is conducted by pediatric department of our hospital. Every week around 30 pediatric patients suffering from different types of seizure are visiting for treatment at “epilepsy clinic.” No study was carried out for drug utilization of ASDs at our setup, so we decided to undertake study by keeping primary objective, to know drug

utilization pattern of ASDs in pediatric patients suffering from various types of seizure and secondary objectives were to study the utilization pattern of drugs other than ASDs and to monitor the adverse drug reactions (ADRs) associated with the use of ASDs.

METHODS

This study was approved by the Institutional Ethics Committee (Approval number: MCLJ/IEC/169/2010), Shree M.P. Shah Government Medical College and Guru Gobind Government Hospital, Jamnagar. Study was Cross-sectional, observational and single centered and carried out over a period from February 2011 to April 2012 in 430 pediatric patients. Pediatric patients up to 15 year, of either sex, attending "epilepsy clinic" for treatment of seizure and whose written informed consent were obtained from parents or guardian after explaining in simple and vernacular language by the principal investigator, were included in the study and patients of >15 year & patients who were not willing to take part in the study were excluded. Descriptive statistical analysis was done using MS Excel and GraphPad Prism. Data analysis included patient indicators, prescribing indicators & ADR profile.

- A. Patient indicators include:
 1. Age: Average age of boys and girls
 2. Sex: Total number of boys and girls
 3. Educational status (of patients >5 years of age)
 4. Immunization status (Yes: Complete or incomplete/ No).
- B. Diagnosis (EEG/magnetic resonance imaging [MRI]/ computed tomography [CT]) & types of seizure
- C. Prescribing indicators include:
 1. Average number of ASDs & total drugs prescribed per patient. This is calculated as:
 - Average number of ASD's/patient = Total number of ASD's prescribed for all patients/ Total number of patients
 - Average number of total drugs/patient = Total number of drugs prescribed for all patients/ Total number of patients
 2. Most commonly prescribed ASD and the most common drug(s) prescribed for each seizure type
 3. Prescribing pattern of ASDs (primary/add on)
 4. Percentage of prescribing ASD (monotherapy/polytherapy)
 5. Percentage of ASDs prescribed using generic name/ brand name
 6. Percentage of prescribed ASDs included in the national list of essential medicines (EML) 2011 & World Health Organization (WHO) model list 2011
 7. DU 90% (number of ASDs account for 90% of total prescriptions)
 8. Utilization pattern of drugs other than ASDs for other diseases such as cough & cold, fever, body ache, etc.
- D. ADR profile includes:
 1. Causality, preventability and severity assessment of ADRs
 2. Analysis of drugs responsible for ADRs.

RESULTS

For this study, a total of 430 pediatric patients were included after ruling out exclusion criteria's. Demographic data revealed, out of 430 patients, maximum 300 (69.8%) were boys followed by 130 (30.2%) girls (girl to boy ratio was 2.3:1) and maximum patients 195 (45.3%) belonged to age group 6-10 year which include 137 boys and 58 girls followed by 142 patients (33%) in 11-15 year age group. Mean age was 8.64 ± 3.7 year. History of complete immunization was noted in 371 (86.3%) patients and positive family history of seizure was found in 69 (16%) patients.

The etiologies of seizure are summarized in Figure 1. Among structural etiologies, most common was cerebral palsy (17) followed by temporal lobe epilepsy (13) and gliosis of various regions of cerebrum (13). Among infectious etiologies, most common was TB meningitis (2) and neurocysticercosis (2). Tuberos sclerosis (4) was the most common among genetic etiology.

Out of 430 patients, 65 patients (15.1%) were diagnosed with specific syndromes. The most common syndrome was rolandic epilepsy in 19 (4.4%).

EEG was done as a diagnostic tool in 358 (83.3%) cases while MRI and CT scan was carried out in 92 (21.4%) and 45 (10.5%) patients, respectively.

Among total 430 pediatric patients, 268 (62.3%) patients were having focal seizure, 124 (28.9%) patients were having generalized seizure, 38 (8.8%) patients were falling in unknown category. Types of seizure are summarized in Table 1. Average number of ASD's/patient was 1.334 and the average number of total drugs/patient was 2.26.

Among 268 patients of focal seizure, primarily prescribed drug was carbamazepine in 198 (73.8%) patients followed by sodium valproate in 58 (21.6%) cases. In 95 patients of focal seizure, eight different ASDs were prescribed as add on therapy, out of those levetiracetam was selected add on ASD in 30 (11.1%) patients followed by clobazam in 22 (8.2%) patients, topiramate in 20 (7.5%), etc. Among 124 patients suffering from generalized seizure, primarily prescribed

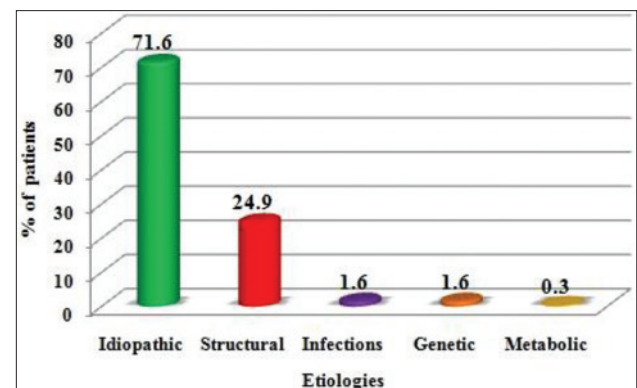


Figure 1: Etiologies of seizure.

Table 1:Types of seizure.

Diagnosis	No. of patients (%)
1. Focal seizure	268 (62.3)
Focal seizure with/without dyscognitive features	243 (56.5)
Focal seizure evolves to bilateral, convulsive	25 (05.8)
2. Generalized seizure	124 (28.9)
Tonic clonic seizure	103 (24)
Myoclonic seizure	11 (02.6)
Absence seizure	8 (01.8)
Atonic seizure	2 (0.5)
3. Unknown	38 (8.8)
Epileptic spasm	14 (3.2)
Others	24 (5.6)
Total	430 (100)

drug was sodium valproate in 111 (89.5%) patients followed by carbamazepine in 13 (10.5%) and in 26 patients of generalized seizure were prescribed six different ASDs as add on therapy, most common was lamotrigine in nine (7.3%) patients followed by clobazam in seven (5.6%) patients, etc. In 14 patients with infantile spasm, sodium valproate was the drug of choice in 12 (85.8%) patients and nitrazepam (35.7%) was the most common ASD prescribed as add on treatment. 24 patients were having unclassified seizure, sodium valproate was prescribed as primary treatment in 17 (70.8%) patients followed by carbamazepine in seven (29.2%) patients and clobazam was most common add on treatment in four (16.7%) patients. We observed that different 14 ASDs were prescribed in 430 pediatric patients suffering from different types of seizure which include carbamazepine (225, 39.2%), sodium valproate (210, 36.6%), followed by clobazam (38, 6.6%), levetiracetam (33, 5.7%), topiramate (24, 4.2%), lamotrigine (13, 2.3%), etc. Prescribing pattern of ASDs is summarized in Table 2.

Majority of patients, 316 (73.5%) were prescribed single ASD while remaining patients were on polytherapy. This is summarized in Figure 2. Most commonly prescribed single drug therapy (monotherapy) was carbamazepine in 219 (50.9%) patients followed by sodium valproate in 198 (46%) patients. Most commonly prescribed two drug therapy was carbamazepine with levetiracetam in 16 patients out of 87 patients and most commonly prescribed three drug therapy was (valproate + carbamazepine + clobazam) in three patients out of 24 patients.

In 88.7% patients, ASDs were prescribed by generic name. In 78.4% of patients, ASDs prescribed were included in national EML 2011 and WHO model EML for children, 2011. Carbamazepine in (225), sodium valproate in (210), clobazam in (38) and levetiracetam in (33), were accounted for more than 90% of total ASDs used. Among utilization of drugs other than ASDs, 1st most commonly

Table 2: Prescribing pattern of ASDs in different types of seizure.

Type of seizure	Primary ASD (%)	Add on ASD (%)
Focal seizure	Carbamazepine (73.8)	Levetiracetam (11.1)
Generalized seizure	Sodium valproate (89.5)	Lamotrigine (7.3)
Infantile spasm	Sodium valproate (85.8)	Nitrazepam (35.7)
Unclassified/ unknown	Sodium valproate (70.8)	Clobazam (16.7)

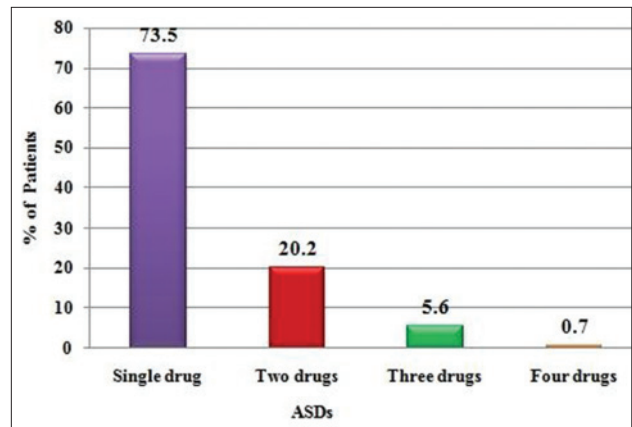


Figure 2: Percentage of patients prescribing monotherapy & polytherapy.

prescribed group of drugs was antipyretic in 133 (64.6%) patients with paracetamol being the most common one followed by 2nd most common group of antihistaminics in 119 (57.8%) with cetirizine being most common and 3rd group of antimicrobials in 45 (21.9%) with amoxicillin and azithromycin being most common. Most of ASDs were in the recommended dose range, in our study, we have observed that sodium valproate was prescribed in range of 5-60 mg/kg, carbamazepine was prescribed over a range of 5-40 mg/kg.

Total 118 ADRs were observed in 112 (26%) patients out of 430 patients, six patients were having two ADRs together. ADRs were most common in the age group 11-15 year (48, 42.9%) followed by 6-10 year (45, 40.2%) and in boys (80, 67.8%) followed by girls (38, 32.2%). Most common ADR was irritability in 38 (32.2%) patients that was mainly due to carbamazepine (19) and sodium valproate (18) followed by drowsiness in 22 (18.6%) patients, mainly due to sodium valproate (13). Most common drug involved in ADR was sodium valproate in 24.3% patients followed by carbamazepine in 19.1% patients. As per WHO causality assessment scale, relationship between the ADRs and the respective drugs comes under "possible" category in 103 (87.3%), whereas "probable" in 15 (12.7%). As per Hartwig & Siegel severity assessment scale, relationship between the ADRs and the respective drugs comes under

“mild” category in 112 (94.9%) and “moderate” category in 6 (5.1%). As per Schumock and Thornton preventability assessment scale, 116 ADRs were preventable (98.3%). Except in six cases (2-weight gain, 2-rash, 1-blurring of vision, 1-Steven Johnson syndrome), the treatment with ASD was continued in all patients who reported ADRs because seizure were well-controlled and ADRs did not significantly disturb the normal activities of patients. Assessment of ADRs is summarized in Tables 3 & 4.

Table 3: Causality, severity, preventability assessment of ADRs and sex wise distribution (n=112) in patients receiving ASDs.

	No. of reactions	Percentage
1. Sex		
Boys	80	67.8
Girls	38	32.2
2. Causality assessment		
Possible	103	87.3
Probable	15	12.7
3. Severity assessment		
Mild	112	94.9
Moderate	6	5.1
4. Preventability assessment		
Preventable	116	98.3
Nonpreventable	2	1.7

Table 4: ADRs with ASDs.

ADR	No. of patients with ADRs (%)
Irritability	38 (32.2)
Drowsiness	22 (18.6)
Tiredness	12 (10.2)
Anorexia	10 (8.5)
↓ Concentration & memory	7 (5.9)
Weight gain	7 (5.9)
Dizziness	5 (4.2)
Weight loss	2 (1.7)
Anxiety	2 (1.7)
Blurring of vision	2 (1.7)
Rash	2 (1.7)
Alopecia	2 (1.7)
Tremor	1 (0.8)
Confusion	1 (0.8)
↓ Sleep	1 (0.8)
Gum hypertrophy	1 (0.8)
Headache	1 (0.8)
↓ Sweating/hypohydrosis	1 (0.8)
Stevens johnson syndrome	1 (0.8)
Total	118 ADRs

DISCUSSION

Pediatric patients are anatomically and physiologically different from a normal healthy adult in terms of weight and surface area. The physiological systems are also in growing phase that contribute to differences in the rate and extent of drug absorption, metabolism, excretion (pharmacokinetics) as well as pharmacodynamic effect as compared to normal healthy adult. Concomitant diseases and drugs may complicate pharmacotherapy.⁵ Limited access of services, low education level, lack of good knowledge about epilepsy, limited finances, and lack of insurance make clinical management of pediatric epilepsy a serious problem in a developing country.⁶ Thus, it is important to monitor dose, dosage formulation, route(s) of administration and ADRs for treatment, and control of epilepsy in pediatric patients.

In this study, maximum patients 45.3% belonged to age group 6-10 year with a mean age 8.64 ± 3.7 year. This is in consonance with study carried out in Malaysia⁷ and maximum pediatric patients 69.8% were boys (girl to boy ratio was 2.3:1). This is in consonance with a study conducted in Khartoum.⁸ History of complete immunization were noted in 86.3% patients, immunization is one of the important factors for primary prevention of epilepsy because immunization against vaccine preventable diseases like measles, diphtheria, pertussis, tetanus, etc., reduces brain damage as well as infection-related febrile episodes that carry a risk of febrile convulsions.⁹ In educational status, 71.8% patients were attending school regularly. Repeated seizures discourage parents to enroll children to school and may also lead to irregularity in education. Seizures are known to affect personality and may affect the study.¹⁰ Positive family history of seizure was found in 16% of patients. It is reported that epilepsy is a hereditary disorder family history and genetic predisposition lead to increased risk of epilepsy in child.¹¹ Majority of patients 71.6% had no specific cause of seizure. This is in accordance with pharmacoepidemiological study from Oman.¹² EEG was done as a diagnostic tool in 83.3%. American academy of neurology guideline for epilepsy recommended EEG as a part of routine neurodiagnostic evaluation for diagnosis and types of epilepsy though neither normal nor abnormal EEG alone excludes or confirms the diagnosis of epilepsy, also suggests diagnostic use of CT and MRI,¹³ but in our study, MRI and CT scan was carried out in 21.4% and 10.5% patients, respectively, this may be because of our hospital is a government hospital and the majority of our patients were from lower socio-economic class. The International League against Epilepsy classification of epilepsy and epileptic syndromes is useful for proper diagnosis and to outline management.¹⁴ Out of 430 patients, 62.3% patients were having focal seizure, 28.9% patients were having generalized seizure and remaining 8.8% patients were falling in unknown category. Present study and other studies conducted at Malaysia and Sweden clearly showed that focal seizures are a major type of seizure.^{7,15} While in Oman study, generalized seizure were observed in the majority of cases in pediatric patients,¹² that contradicts

finding of our study, it may be due to racial, ethnic or genetic difference of various regions. 15.1% of patients were diagnosed with specific syndromes, most common syndrome was rolandic epilepsy, this is in consonance with the study conducted in Sweden.¹⁵

Carbamazepine was drug of choice in 73.8% patients suffering from focal seizure; sodium valproate was drug of choice in 89.5% patients of generalized seizure, 85.8% patients of infantile spasm and 70.8% patients of unclassified seizure. Our results are in accordance with pediatric DUS of ASDs from Malaysia.⁷ Guidelines for the treatment of pediatric epilepsy recommend sodium valproate for the patients of generalized seizure and carbamazepine for the patients of focal seizure.^{16,17}

In our study, carbamazepine and sodium valproate were prescribed as a primary ASD in 96.98% patients. Other studies conducted at Taiwan and India^{18,19} clearly showed that carbamazepine was most commonly used ASD. In our study, second most common ASD was sodium valproate whereas in other two studies,^{18,19} phenytoin was second most common ASD, because of increasing in awareness about ADRs of these two drugs, availability of less toxic and equally effective ASDs may lead to decrease utilization of phenytoin and phenobarbital in pediatric patients.²⁰ Newer ASDs such as levetiracetam, clobazam, topiramate, lamotrigine, and clonazepam were prescribed as add on drugs. We also found that in our study and Swedish study Clobazam was commonly used as add on ASD.¹⁵ In our study, we have found that out of total prescribed ASDs, >90% were conventional ASDs e.g., sodium valproate, carbamazepine, phenytoin, and phenobarbital while newer ASDs such as clobazam, lamotrigine, topiramate, oxcarbazepine, levetiracetam, and vigabatrin prescribed only in a limited number of patients as an add on ASD where seizure were not controlled with single ASD. Various studies from developing countries like India and Sri Lanka reported use of conventional ASDs in the majority of cases as compared to newer ASDs in patients suffering from epilepsy.^{19,21} Conventional ASDs are effective and quite cheaper than newer ASDs. In addition to that, newer ASDs are not included in WHO model EML 2011 and national EML 2011.^{22,23} Patients included in our study were mainly from lower socioeconomic class, may explain greater use of conventional ASDs.

Single ASD (monotherapy) was prescribed to 73.5% patients and most common was carbamazepine 50.9% followed by sodium valproate. Findings of our study are in consonance with findings of the study conducted in Coimbatore.²⁴ It indicates that in our study, there is very less degree of polypharmacy. Majority 88.7% of ASDs were prescribed by generic name; this confirms the trend of prescribing drugs by generic name is high in our set up which is one of the government hospitals where most of the patients come from lower socio-economic class. Sometime generic product of few ASDs is not available in hospital pharmacy due to short supply, shows that patients are put to financial loss by the use of brand name drugs.

In 78.4% of cases, ASDs prescribed were included in WHO model EML for children and EML, 2011.^{22,23} It shows that ASDs treatment in our hospital was closely follows the guideline mentioned in national EML (2011) and WHO model EML (2011). While ASDs prescribed which are not included in EML were only used as add on ASDs for uncontrolled seizure hence it is logical to assume that drug treatment of seizure is much more rational.

Carbamazepine, sodium valproate, clobazam, and levetiracetam were accounted for more than 90% of total ASDs used. The DU 90% is an inexpensive, flexible, and simple method for assessing the quality of drug prescribing for health care. Adherence to prescription guidelines and the total number of products in the DU 90% may serve as general quality indicators. As per various guidelines sodium valproate and carbamazepine are the primary drugs in any epilepsy and clobazam is indicated for add on ASD.^{16,17} Among utilization pattern of other drugs, antipyretic group of the drug was most commonly prescribed followed by antihistaminics and antimicrobials. We found that among those prescribed drugs, there is less risk of interaction with various ASDs.²⁵

In analysis of ADRs of ASD, 118 (26%) ADRs were noted in total 430 patients whereas in a study conducted at Kathmandu, it was reported in 35.13%.²⁶ ADRs were most common in the age group 11-15 year and in boys. In our study, we found that most common ADR was irritability in 32.2% patients followed by drowsiness and most common drug involved in ADR was sodium valproate followed by carbamazepine whereas in a study conducted at Hyderabad, drowsiness was most common ADR and carbamazepine and phenytoin were most common drugs responsible for ADRs.²⁷ It may be due to different prescribing pattern of ASDs in different types of seizure. As per WHO causality assessment scale,²⁸ relationship between the ADRs and the respective drugs comes under "possible" category in 87.3%. As per Hartwig & Siegel severity assessment scale,²⁹ relationship between the ADRs and the respective drugs comes under "mild" category in 94.9%. As per Schumock and Thornton preventability assessment scale,³⁰ 98.3% ADRs were preventable. Increase awareness of ADRs by applying active pharmacovigilance system in our set up and use of more effective and safer ASDs in the majority of patients has decreased number of ADRs in our study compare to study carried out at Kathmandu.²⁶

CONCLUSION

In our study, focal seizure was the most common type followed by generalized seizure with no specific cause of seizure in the majority of pediatric patients. Seizures were more common in boys and in 6-10 year age group. Monotherapy was most frequently used in all types of seizure with carbamazepine being most common in focal and sodium valproate in generalized seizure. The drugs prescribed were mainly from the essential drug list and by generic names. The ADRs were predominant in boys of age group 11-15 year

and found to be mild and preventable in the majority with most common being irritability.

There is lack of data, at our setup and also in India, about utilization of ASDs in pediatric patients suffering from different types of seizure. Despite several limitations (limited sample size, shorter duration of study, unavailability of utilization pattern and ADRs of newer ASDs, dose of drugs were based on mg/kg so cost analysis was not done), our study made several important conclusions.

- Availability of drugs and therapeutics committee and of a formulary can further help to improve prescribing pattern of the prescribers and increase awareness of ADRs due to ASDs.
- Availability of therapeutic drug monitoring should be there particularly in cases of uncontrolled seizure.
- Quality-of-life of many epileptics in developing countries can be improved, if the local production of commonly used efficacious conventional ASDs is increased and to cut down the cost involved in importing new ASDs.
- Pharmacovigilance work should be carried out with more active efforts that might be helpful for better management of patients with effective and safer ASDs that decreases the incidence of ADRs with their use.

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