



## THE PATTERN OF ANTISEIZURE DRUGS, THEIR UTILIZATION AND THEIR ADVERSE EFFECTS IN PEDIATRIC POPULATION- A PROSPECTIVE STUDY.

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**ABSTRACT** **BACKGROUND:** Antiepileptic drugs (AEDs) are commonly used drug for epilepsy. 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. **AIMS AND OBJECTIVE:** The objective was to study the utilization pattern of antiepileptic drug and their adverse reactions (ADRs) in pediatric outpatients in epilepsy clinic. The study was performed with an aim to study the utilization pattern of anti-epileptic drugs (AEDs) for the pediatric patients suffering from various forms of epileptic seizures. **MATERIAL AND METHODS:** This prospective, observational study was conducted for a period of one year six months in Pediatric outpatient department in epilepsy clinic in Santosh medical college and hospital from July 2008 to December 2009. The data collected from 50 children at the end of the study, were compiled in a specially designed data form and were analyzed. **RESULT:** The distribution of pediatric seizures was found to be high in male children (58%) and in the age group of 2 to 5 years (42%). The majority of the children (66%) were diagnosed with Generalized Tonic-clonic seizures. Sodium valproate was the commonly prescribed AED in all forms of seizures followed by Carbamazepine (14%), Phenobarbitone (3%) and Phenytoin Sodium (3%). AEDs were mostly prescribed as Monotherapy (78%). An adverse reaction noted during this study was minimal (8%). **CONCLUSION:** Sodium valproate, a conventional AED still remains the commonly prescribed AED for all types of seizures in children aged 2 to 16 y and also was found to be effective and safe.

**KEYWORDS :** Anti-Epileptic Drugs (AEDs), Seizure disorder, Drug utilization study (DUS), Adverse Reactions (AR).

### INTRODUCTION:

Epilepsy is the most common neurological disorder characterized by recurrent seizures due to abnormal excessive synchronous neuronal activity in the brain [1, 2]. Epilepsy affects 0.5 to 1% of the world's population (50 million people worldwide). 1 in 26 people will develop epilepsy in their lifetime. [3]. It is estimated that the overall prevalence of epilepsy in India is 5.59 – 10 per 1000 [3]. In most cases, epilepsy has no identifiable cause (idiopathic). Other underlying causes include genetic abnormality and secondary to head injury, infections, ischemia, mass lesions or exposure to drugs and toxins [1, 4].

Drug utilization study (DUS) is defined as “the marketing distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences” [5]. It is, therefore, a study designed to describe quantitatively and a qualitatively-the population of users of a given drug (or a class of drugs like anti-epileptic drugs) and/or the conditions of use (for e.g., indications, duration of treatment, dosage, previous or associated treatments and compliance) [6]. The beginning of DUS can be traced back to the early 1960's. Studies on prescription habits [7] aim to analyze the type of drugs prescribed, their dosing schedule and the adequacy of the prescription for a specific diagnosis. Drug utilization studies are powerful exploratory tools to ascertain the role of drugs in society. They create a sound socio-medical and health economic basis for health care decision making [8]. It is also important to realize that inappropriate use of drugs represents a potential hazard to the patients and an unnecessary expense [9]. Uncontrolled seizures are associated with physical and psychosocial morbidity, dependent behavior, poor quality of life and an increased risk of sudden unexpected death. Therefore treatment with antiepileptic drugs (AED) is mandatory once the patient is diagnosed to be a case of epilepsy [10]. Antiepileptic drugs (AEDs) are the mainstay of the therapy for epilepsy, despite the development in recent years of new therapeutic options, such as brain stimulation or surgery. In the last years, several pharmaco epidemiological studies documented a growing trend in AED use, particularly in elderly patients [11].

### AIMS AND OBJECTIVE:

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. Present study was performed with an aim to study the utilization pattern of anti-epileptic drugs (AEDs) for the pediatric patients suffering from various forms of epileptic seizures.

### MATERIAL AND METHODS:

The present study focused on the prescribing pattern of Anti-epileptic

drugs (AED's) for various seizures occurring in children of either sex aged 2 to 16 years, treatment outcomes and associated adverse reactions (ADR). 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.

The antiepileptic drugs are of two categories namely conventional drugs like sodium valproate, carbamazepine, Phenobarbitone, phenytoin sodium and newer drugs like topiramate, lamotrigine, oxcarbazepine etc. Adjuvant drugs like benzodiazepines are also used in this treatment. An appropriate AED should possess the following features: 1. Achieve complete seizure control using a single drug. 2. To use the most appropriate formulation to ensure that the child can take and absorb the medication. 3. Economically affordable to the patient. 4. Long-term effects on growth and development of the child and short-term effects on behavior, intellectual function and pattern of sleep should be taken care of. This study was a prospective longitudinal study, conducted for a period of 8 months from August 2008 to March 2009 among children attending Pediatric neurology outpatient Department in Santosh medical college, Ghaziabad, U.P. Prescribing pattern of AED was assessed per WHO indication of drug utilization study. The approval for this study was obtained from Institutional Human ethical committee. Each child had a minimum of 5 to 6 visits during the study period of 8 months.

Following data were collected and recorded in a specially designed data entry form during each visit. During the study period, the pattern of usage of antiepileptic drugs [AED's] was evaluated based on following tools.

1. The pattern of drug use among epileptic children defined by age and sex.
2. The relationship between the prescribed medicine and the apparent indications.
3. Type of epilepsy most frequently treated.
4. Utilization pattern of AEDs as Monotherapy and Polytherapy.

### The adverse reactions (ADR) of prescribed AEDs during the study period were analyzed on the following criteria.

1. The incidence and type of adverse drug reaction.
2. The causality relationship of ADR with suspected drug according to Naranjo ADR probability scale.
3. Whether the suspected drug was dropped after the ADR and if any treatment was given for the ADR
4. The drug most commonly causing ADRs, the incidence and type of adverse drug reaction.

**INCLUSION CRITERIA:**

Children age 2 – 16 years are included in this study.

**EXCLUSION CRITERIA:**

Cases of Status Epilepticus and children not willing for the study were excluded. Patients of >16 year & Patients refused to give written consent who were not willing to take part in the study were excluded.

**STATISTICAL ANALYSIS:**

An observational study was done. A descriptive statistical analysis was applied in the present study. Statistical analysis was done using MS Excel and Graph Pad Prism.

**RESULT:****TABLE: 1**

Out of 50 children, 28 were male (56%) and 22 were female (44%). Maximum children were between the age group of 2–5 years (42%). As per table 1, the incidence of epilepsy was more common among male children (56%) compared to female children (44%).

**Table 1: Shows the demographic characteristics of epileptic children**

Age group in years	Male children n (%)	Female children n (%)	All children n (%)
2-5	10 (20%)	11 (22%)	21 (42%)
6-10	14 (28%)	6 (12%)	20 (40%)
11-16	4 (8%)	5 (10%)	9 (18%)

**TABLE: 2**

Shows, the majority of the children (66%) suffered from Generalized Tonic-Clonic seizures. Three children had myoclonic seizures (6%) and four had absence seizures (8%). The partial simple type was observed in three children (6%). Febrile seizures were noted in 7 children (14%). Sodium valproate was used AED (57.57%) in most forms of seizures, both as Monotherapy and Polytherapy. Carbamazepine (CBZ) (11%) and phenytoin sodium along with sodium valproate and phenobarbitone were 9% and 6% respectively. Absence seizures were treated with sodium valproate only. Sodium valproate and Carbamazepine was prescribed for myoclonic seizures. Oxcarbazepine was the only AED used for both cases of Simple partial seizures. The majority of the children with febrile convulsions were treated with Clobazam alone (42.85%). Clobazam in combination with phenobarbitone and sodium valproate were prescribed for 14.28% of febrile convulsions.

**Table 2: Shows the type of epilepsy and the prescribed medicine**

Type of epilepsy	No. of cases n (%)	Prescribed medicine-n (%)
<b>Generalized Tonic-clonic</b>	33(66%)	Sodium valproate-19(57.57%)
		Carbamazepine-3 (9.09%)
		Sodium valproate+ Phenytoin sodium- 3 (9.09%)
		Sodium valproate Carbamazepine- 4 (12.12%)
		Sodium valproate+topiramate-2(6.06%)
		Phenytoin sodium+Phenobarbitone- 2(6.06%)
<b>Generalized myoclonic</b>	3 (6%)	Sodium valproate-2 (66.66%)
		Carbamazepine-2 (66.66%)
<b>Generalized Absence</b>	4 (8%)	Sodium valproate-1 (25%)
<b>Partial simple type</b>	3(6%)	Oxcarbazepine-1 (33.33%)
<b>Febrile convulsions</b>	7 (14%)	Clobazam-3 (42.85%)
		Sodium valproate-2 (28.57%)
		Phenobarbitone- 2 (28.57%)
		Clobazam+ Sodium valproate-1 (14.28%)
		Clobazam+Phenobarbitone-1 (14.28%)

**Table-3:** As per table 3, 39 children (78%) were treated with AEDs as Monotherapy and 7 children (14%) received two drug therapies while four children (8%) had three drug therapy.

**Table 3: Shows the utilization pattern of AEDs as Monotherapy and Polytherapy**

Drug therapy	No. of patients	Percentage
Monotherapy	39(50)	78%
Two drug therapy	07(50)	14%
Three drug therapy	04(50)	8%

**Table: 4**

Sodium valproate was associated with adverse reactions in 3 children (6%) as per table 4. One adverse reaction was observed in a case treated with phenytoin sodium (2%). Change of AED was required in two cases (4%) treated with sodium valproate.

**Table 4: Shows the observed adverse reactions**

No. of patients	ADR reported	Suspected drug	Casualty relationship	Whether treatment with AED continued/stopped
3	Hyperactivity	Sodium Valproate	Possible	Stopped
1	Behavioral disturbances	Phenytoin	Possible	Stopped
1	Weight gain	Sodium Valproate	Possible	Continued
1	Sedation	Sodium Valproate	Possible	Continued
1	Oral ulcers	Sodium Valproate	Possible	Continued

**DISCUSSION:**

The present study shows that major incidence of childhood seizures occurs in male children (56%) which correlate with the results of previous epidemiological studies conducted in India, Malaysia, and Oman [12-14] except for a study in Pakistan by Aziz et al. [15] who contradicts this picture. It has been scientifically proved that female sex hormones (estrogen and progesterone) affect the threshold of seizures to some extent which leads to the difference [16]. The incidence of epilepsy has a bimodal distribution with a peak in the first decade and a second peak in elderly which is also proven in this study as there is a maximal incidence before 10 y (82% children <10 y). The distribution of seizures was found to be high in the 2-5 age groups of children (42%) in this study. DR. O P GHAI, an eminent Pediatrician makes a note in his Textbook "the incidence of epilepsy is high in preschool years" [17] and our study confirmed it. The age distribution has a critical importance in DUS as it gives an idea whether drug treatment varies according to different age groups. Generalized tonic-clonic seizures were the commonest form of seizures (66%) observed in children between 2-16 y in our study. A majority of previous clinical studies like Shaheen Usman et al. [18] have shown the dominance of this seizure type in children while a study conducted in Coimbatore private hospital in south India [19] contradicts by concluding that simple Partial seizures and generalized myoclonic were observed as (6%) in children below 16 years. Jincy George and Julia [20] also conclude that 51% of their pediatric study group was of the general type of epilepsy. Nelson's textbook of pediatrics also says about the dominance of GTCS in children [21]. In our study, other types of generalized seizures (tonic clonic and myoclonic) were observed in 72% and Febrile convulsions in 14% of children. Febrile seizures have been reported to be one of the most common causes of seizure attacks in children. Febrile convulsions are the commonest provoked seizures and 3-5% of children experience them between 6 months to 5 years [22]. In our study, seven children with febrile seizures had incidence before 3 y of age. Sodium valproate was found to be the most commonly prescribed AED (57.57%) as against other conventional AED's like Phenytoin Sodium (6%), and phenobarbitone (6%) in our study. The current NICE guidelines [22] advise either CBZ (partial type) or Sodium valproate (partial or generalized) as the first line of therapy for epilepsy. Hence, the broad usage of Sodium valproate in this study has followed the guidelines. Sodium Valproate was effective with less adverse effects in all forms of seizures except simple partial type where oxcarbazepine was used. Sodium valproate was used as Monotherapy (57.57%) in the majority of cases. The increase in dose of Sodium valproate was required in 3 cases (12%) of tonic-clonic seizures. Loscher, 2002 has quoted in his book "Basic Pharmacology of valproate" after a clinical experience with sodium valproate for 35 y in the treatment of Epilepsy [23] that Sodium valproate has a broad spectrum of anticonvulsant activity, although it is primarily used as a first line treatment for Tonic-clonic, absence and myoclonic seizures

and used as a second line treatment for partial seizures and infantile spasms. Valproate and phenobarbitone have favorable pharmacokinetics in children, whereas carbamazepine and phenytoin have unfavorable kinetics as per Glauser TA et al. in 2013 [24] Antiepileptic drug utilization and seizure outcome among pediatric patients in a Malaysian hospital in 2010 [18] conclude that valproate was the most commonly used drug (37%) followed by carbamazepine (28%). A metacentric study conducted in Bagalkot, Karnataka 2015 concludes that conventional AEDs was more effective in terms of reduction of seizures and are mostly used as Monotherapy [25]. Phenytoin was the most commonly used AED followed by valproate as per their conclusion which contradicts the results of our study.

### CONCLUSION:

Sodium valproate can be used as the first-line drug in all forms of generalized seizures and as a continuous prophylactic in febrile seizures. Side effects were minimal and Compliance was good in most of the children. Monotherapy was followed mostly in the treatment of pediatric seizures. Sodium valproate can be used as the first-line drug in all forms of generalized seizures and as a continuous prophylactic in febrile seizures. Side effects were minimal and Compliance was good in most of the children. Monotherapy was followed mostly in the treatment of pediatric seizures. There was a rational prescription of AEDs in all children. This drug utilization study in pediatric neurology department gives an insight into current pharmacotherapy practices in childhood seizures. Limitations are data from an Out Patient department with a small sample size. Hence, the findings cannot be generalized.

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