

**Original article:**

## **Drug Utilization Study of Antiepileptic Drugs in Pravara Rural Hospital, Loni, Ahmednagar, India –A Retrospective Study**

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### **Abstract:**

**Introduction:** An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Depending on the location and the mode of onset of seizure in the brain, seizures are mainly classified as generalized and focal seizures. Generalized epileptic seizures are further categorized as: tonic-clonic seizures, absence seizures, myoclonic seizures, clonic seizures, tonic seizures, and atonic seizures and infantile spasm.

**Material and methods:** This study was conducted for the period of 2 years from October 2016 to October 2018. Case collection was done during first 18 months of the study. The study was approved by IEC. Last 6 months were reserved for analysis and integration of the collected data and interpretation of results. Only people with epilepsy and treated with an AED are included in this study.

**Results:** Out of 200 subjects in this study 138 subjects have experienced adverse drug reactions to given drugs. Of all 155 subjects, large number of subjects have suffered Drowsiness, fatigue and tiredness, memory problem, Headache, Irritability, Disturbed sleep gastrointestinal problems. It has also been observed that, these adverse drug effects were most common in patients taking Polytherapy.

**Conclusion:** In our study Partial epilepsy was the commonest type of epilepsy recorded followed by generalised seizures. Most of patients are either young or above 50 years and epileptic seizures are more common in man but not by the large margin of difference.

**Keywords:** Antiepileptic Drugs , epileptic seizure.

### **Introduction:**

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.<sup>1,2</sup> Depending on the location and the mode of onset of seizure in the brain, seizures are mainly classified as generalized and focal seizures. Generalized epileptic seizures are further categorized as: tonic-clonic seizures, absence seizures, myoclonic seizures, clonic seizures, tonic seizures, and atonic seizures and

infantile spasm.<sup>3</sup>The clinical manifestation of these seizures may vary from mild alterations in consciousness to convulsions.<sup>3</sup>

Globally it is estimated that approximately 70 million people have epilepsy and the prevalence of epilepsy is 5-9 per 1,000 population.<sup>4,5</sup> India the prevalence rate of epilepsy among adults and elderly varied from 1.2 to 11.9 per 1,000 population.<sup>6</sup> The estimated rural rate was 4.8 per 1,000 and the urban rate was 2.5 per 1,000, male and female was 4.9 per 1,000 and 3.9 per 1,000, respectively.<sup>7</sup>

The cause of epilepsy differs person to person. It can be acquired for example Head Injuries, Brain Infections, hippocampal sclerosis, Brain tumours, Stroke, Or genetic Eg: Dravet syndrome or Metabolic or infectious.<sup>8</sup>

The epilepsy can be diagnosed Clinically and detailed by using Electroencephalogram (EEG), Computer Tomography (CT), Magnetic Resonance Image (MRI) of brain, symptomology.<sup>11</sup> The ultimate goal of the treatment was minimizing the side effects of the drugs, improving the quality of the life.<sup>9</sup>

Many drugs are currently available for the treatment of epilepsy. These AEDs share three basic mechanisms of actions. They either reduce repetitive firing due to interference with sodium currents, augment  $\gamma$ -amino butyric acid (GABA) neurotransmission or reduce transient  $Ca^{++}$  currents.<sup>10</sup> Older/conventional AEDs which were available before 1980 are classified as “first-generation” e.g phenytoin, carbamazepine, valproic acid and ethosuximide, are commonly used as first line drugs. They are relatively less expensive. Drugs like gabapentin, lamotrigine, vigabatrin, topiramate, tiagabine and zonisamide are the newer ones and classified as “second-generation,” and currently used as add-on or alternative therapy. They have lesser adverse effects and have few, if any, drug interactions.<sup>11</sup>

Various demographic and clinical factors affect the treatment and choice AEDs. The factors are age, gender of the patient, type of epilepsy, socioeconomic status of the patient, availability of the medication, special circumstances and side effects of the drugs.<sup>12</sup>

Some ADR's may be common with the AEDs due to the long duration of treatment and multiple drug therapy and include, drowsiness, sedation and Headache. They can be diverse as well, ranging from idiosyncratic reactions like bone marrow depression (carbamazepine) to acute myopia and glaucoma (topiramate). Monotherapy is the usual dictum, but polytherapy is needed for patients with multiple seizure types or refractory disease.<sup>10</sup>

It is difficult to assess accurately the exact incidence of AED related ADRs due to deficient systematic pharmacoepidemiologic studies investigating drug utilization pattern.<sup>13</sup> Our study attempts to analyze the pattern of drug utilization in different types of epilepsy, the broad categories of epilepsy, extent of polytherapy and ADRs (adverse drug reactions) reported by the patients.

#### **Material and methods :**

This study was conducted for the period of 2 years from October 2016 to October 2018. Case collection was done during first 18 months of the study. The study was approved by IEC. Last 6 months were reserved for analysis and integration of the collected data and interpretation of results. Only people with epilepsy and treated with an AED are included in this study. A total of 200 patients who met the inclusion criteria were interviewed and following data were retrieved from the prescription and the patient's medical records: about the demographic data (age and gender), type of epileptic seizure, and concomitant drugs, complete history of presenting illness, past medical history (known

or newly diagnosed epileptic patient), family history, socioeconomic status was calculated after interview of study subjects according to modified kuppusswamy scale, occupational history, AEDs data (i.e. name of drug and formulation, dose, route of administration) and selection of AEDs and adverse drug reaction ( if any) occurred during current therapy and the prescription given to the respective patients were recorded and separated according to the dosage form and class of the drug.

### Statistical analysis

At the end of the present study, the data collected were compiled using Microsoft Excel Worksheet and processed by using appropriate statistical software. The collected data was analyzed statistically using chi-square test. A p-value of less than 0.05 was considered to be statistically significant.

Gender	Number	Percentage
Male	103	51.5
Female	97	48.5
Total	200	100

Age group	Number	Male	Female	Percentage
14-19	43	22	21	21.5
20-29	32	15	17	16
30-39	31	17	14	15.5
40-49	23	13	10	11.5
50-59	26	19	07	13
60-69	34	13	21	17
70 and above	11	4	7	5.5
Total	200	103	97	100

**Table -1: Demographic Characteristics of the study population being treated with AEDs**

**Table -2: Types of epileptic seizure**

Types of seizures	Total	Percentage
Generalized seizures	64	32
Partial seizures	75	37.5
Status epilepticus	02	1
Idiopathic/Unclassified	59	29.5
Total	200	100

Co-morbid conditions	Number	Percentage
Hypertension with or without complication	15	7.5
Diabetes Mellitus	8	4
Cardiovascular accident and related conditions	12	6
Meningitis and other infections	14	7
Alcohol withdrawal	4	2
Others	25	12.5
None	122	61
Total	200	100%

**Table -3: Distribution of study subjects according to associated comorbidity**

Antiepileptic Drug Used	Frequency of drugs used	Males	Females	Percentage %
Phenytoin	127	65	62	37.5
Midazolam	83	43	40	24.4
Levetiracetam	72	30	35	19.1
Carbamazepine	29	15	14	8.5
Valproic acid	15	10	05	4.4
Lorazepam	09	05	04	2.6
Phenobarbitone	8	06	02	2.3
Topiramate	4	0	4	1.2
Total	340	174	166	100

**Table 4: Distribution of study subjects according to Overall Utilization Of AEDs**

Number of AEDs per prescription	Frequency (N) of patients	Percentage (%)	
1	86	43	Monotherapy
2	93	46.5	Polytherapy
3	16	8	Polytherapy
4	5	2.5	Polytherapy
Total	200	100	

**Table -5: Distribution of drugs according to number of AEDs prescribed**

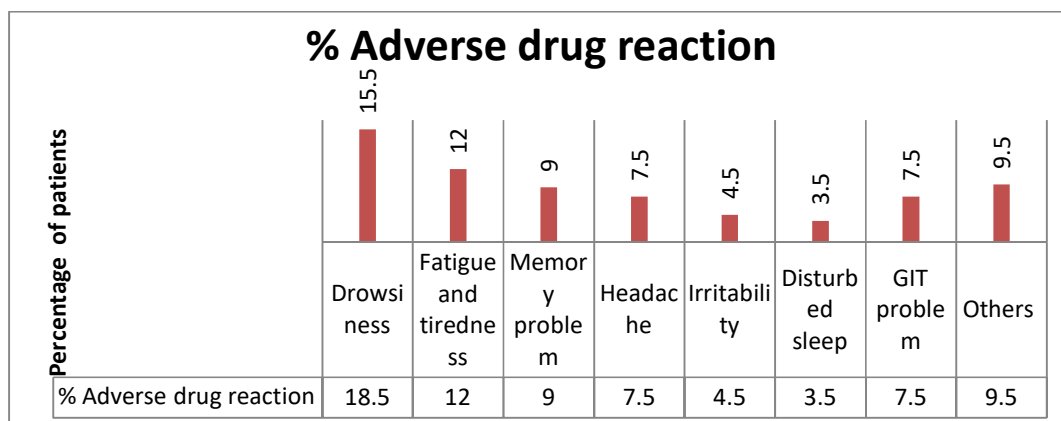
Name of AEDs	No. of drugs	Percentage (%)
Generic name	56	13.46
Brand name	343	82.45
Generic and brand	17	4.09

**Table -6: Distribution of drugs prescribed based on generic and brand names**

Type of AEDs use	Frequency (N) out of 340 prescriptions	Percentage (%)
Newer generation AEDs	69	20.3
ADR	Frequency 271	Percentage 79.7
Drowsiness	31	15.5
Fatigue and tiredness	24	12
Memory problem	18	09
Headache	15	7.5
Irritability	09	4.5
Disturbed sleep	07	3.5
GIT problem	15	7.5
Others	19	9.5
Total	138	69
Older/ Conventional AEDs		
Total	340	100

**Table 7: Distribution of study subjects according to generation of AEDs**

**Table -8: Distribution of study subjects according to type of adverse drug reactions**



## RESULTS

Prescriptions originating from 200 patients with a confirmed diagnosis of epileptic seizures and treated with AEDs were collected over two years period. The demographic characteristics of these patients are presented in Table 1. The age ranged from 14 to 76 years with most patients from age group of 14-19 years (21.5%) and 35.5% of people were aged above 50 years. 51.5% of patients encountered were males.

The type of epileptic seizures is presented in Table -2. Partial seizures are the most prevalent of all types of epileptic seizures which accounted in 37.5% of patients.

Table -3 shows most common co-morbid condition was found to be Hypertension with or without complication (7.5%). Second common co-morbid conditions present in study subjects were related to Meningitis and other infection for example Viral encephalitis , Malaria etc. (7%).

For 200 patients of epilepsy 340 times AEDs was prescribed (Table -4). Average number of drugs per prescription was 340/200 i.e. 1.7. Majority of the study subjects, received phenytoin (37.5%) as an emergency medication and for maintenance purpose in respective doses and combination according to symptoms and severity of Epilepsy, followed by Midazolam (24.4%) levetiracetam (19.11%) and other AEDs.

In this study population, 86 (43%) were prescribed an AED as monotherapy and 114 (57%) Polytherapy including 93 (46.5%) needed dual therapy (Table -6). 16 (8%) and 5 (2.5%) patients were managed with 3 drugs an 4 drugs respectively. Most of the polytherapy prescriptions consisted of triple therapy. Only one patient was administered with 4 AEDs.

The most frequently used combination therapy of AEDs consisted of Phenytoin + Midazolam (15%) followed by Phenytoin + Levetiracetam (9.5%) and others.

Most of the AEDs were prescribed by generic names (83%), followed by 13% and 4% of the AEDs which were prescribed by brand name and by both generic and brand name, respectively (Table -6).

We have seen only 2 newer generation antiepileptic agents i.e. levetiracetam and Topiramate which accounted for 20.3% and older generation for 79.7% (Table -7).

Out of 200 subjects in this study 138 subjects have experienced adverse drug reactions to given drugs. Of all 155 subjects, large number of subjects have suffered Drowsiness, fatigue and tiredness, memory problem, Headache, Irritability, Disturbed sleep gastrointestinal problems. It has also been observed that, these adverse drug effects were most common in patients taking Polytherapy.

## DISCUSSION

The gender distribution in this study has shown that 51.5% study subjects were males and 48.5% of the study subjects are females, thus males are observed to be affected more than females, but only by the short range of difference only (**Table 3, Figure 3**). The lack of gender effect on the distribution is consistent with findings from other studies conducted by Radhakrishnan et al (reported a prevalence rate of 5.2 per 1,000 for males and 4.7 per 1,000 for females).<sup>14</sup>. Pandey et al showed females were more frequently attacked with epilepsy than males.<sup>15</sup> Arulkumaran et al. study conducted in Coimbatore, Raina et al and many other studies showed opposite result that males were more frequently attacked with epilepsy than females.<sup>16,17</sup>

We found bimodal distribution of epilepsy incidence with peaks during early life (21.5%, 14-19 years ) and during later part of life (35.5% above 50 years ) . Hauser *et al* and Banerjee *et al* reported Similar kind of data.<sup>18,19</sup>

Most patients were suffering from partial seizures (35.5%) during this period followed by generalized seizures (33%) an Idiopathic/unclassified (29.5%). Mani et al showed similar result.<sup>20</sup>

Present study highlighted that Phenytoin was the most commonly prescribed antiepileptic drug. Similar results were obtained by Shobhana *et al.*, in 2010.<sup>21</sup> Different finding seen in Arulkumaran et al. in Coimbatore study and by Pal et al. in Cuttack, India that showed that sodium valproate was most common AED prescribed. In our study we have found that 43% patients were prescribed monotherapy of AEDs and 57% patients were prescribed polytherapy i.e. > 2 or more antiepileptic drugs .This finding contradicts the finding in study by Shobhana *et al*. The reason for polytherapy may be attributed to higher incidence of refractory epilepsy in our study as Patients included in our study were old patients on antiepileptic drugs for at least 1 year.

Polytherapy can improve seizure control but increases risk of chronic toxicity and drug-drug interaction. It is also associated with a higher cost of medication that decreases Compliance.

In our study it was found that majority (83%) of the AEDs were prescribed by generic names, followed by 13% and 4% of the AEDs which were prescribed by brand name and by both generic and brand name, respectively. A tertiary care rural hospital like ours in India where patients mostly come from the low socioeconomic strata, generic prescribing will substantially reduce the cost of drugs for the patients and subsequently improve compliance.

It was seen in our study that conventional/older AEDs (drugs introduced before 1990) were more frequently prescribed than newer AEDs. Arulkumaran et al.study in Coimbatore also found same. In our study Levetiracetam was only newer antiepileptic used. Other Newer drugs like Lamotrigine, Felbamate, Lacosamide etc are not preferred..

It is very important to compare benefit/risk ratio while prescribing AEDs. In our study most frequently the study subjects have experienced drowsiness, fatigue and tiredness, memory problems, headache and disturbed sleep which were managed by symptomatic medication In the present study, out of 200 subjects in this study 138 subjects have experienced adverse drug reactions/ side-effects to given prescription of drugs. Study by Patel et al 2016 in Gujrat

India also found similar kind of figure. Most frequently the study subjects have suffered drowsiness, fatigue and tiredness, memory problems, headache and disturbed sleep which were managed by symptomatic medication.

### CONCLUSION

In our study Partial epilepsy was the commonest type of epilepsy recorded followed by generalised seizures. Most of patients are either young or above 50 years and epileptic seizures are more common in man but not by the large margin of difference.

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