RESEARCH ARTICLE

Prescription pattern of antiepileptic drugs in seizure disorder, their adverse reactions and cost analysis: A tertiary care hospital-based study

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ABSTRACT

Background: Epilepsy affects 50 million people worldwide and approximately 10 million of these people live in India, but many patients with active epilepsy do not receive suitable treatment for their condition, leading to a large treatment gap. **Aims and Objectives:** This study was conducted to gather baseline information regarding the prescribing pattern of antiepileptic drugs (AEDs) for seizure disorders, adverse reactions, and cost analysis. **Materials and Methods:** It was a prospective study spanning 6 months (January 2019–June 2019), we analyzed the prescription data of 100 patients with seizures willing to give consent. Patients <18 years were excluded from the study. Data obtained were noted and analyzed for demographic profile (gender and age), diagnosis, details of the drugs prescribed, adverse reactions (if any), and cost. **Results:** Out of the 100 patients, generalized tonic-clonic epilepsy was most common (73%) and levetiracetam (36.50%) was the most commonly prescribed AED. About 51% of the patients were given multitherapy and 49% were given monotherapy. About 80.9% of the drugs were prescribed from the National List of Essential Medicines 2015 and 96.10% were prescribed by brand name. The average cost of drug per prescription was 188.58 INR. Cost variation analysis of the two most commonly prescribed drugs was done, levetiracetam, and valproic acid. Cost variation percentage of valproic acid (67.4%) was higher than levetiracetam (49.2%). **Conclusion:** Physician selection of drug depends on several factors such as drug tolerability, patient compliance, efficacy of treatment, and cost of therapy. This study documented a rise in the prescribing trend of newer antiepileptics. The selection of essential drugs was high; however, there is a need to emphasize the concept of prescribing generic medicine among physicians, which will help in lowering the total cost of therapy for patients.

KEY WORDS: Antiepileptic Drugs; Drug Utilization Studies; Adverse Drug Reaction; Cost Analysis

INTRODUCTION

Epilepsy is a chronic neurological disease characterized by recurrent unprovoked seizure affecting roughly 50 million worldwide, of which 80% reside in developing countries.[1] Approximately 10 million people with epilepsy live in India

but many patients with active epilepsy do not receive suitable treatment for their condition, leading to a large treatment gap.[2] The etiology of seizure is multifactorial, including a genetic predisposition for certain seizures, previous head trauma, stroke, brain tumors, alcohol or drug withdrawal, and other conditions. It is proposed to be an interaction between genetically determined seizures thresholds, underlying predisposing pathologies or metabolic derangements, and acute precipitating factors.[3] The overall aim of epilepsy treatment is complete control of seizures, with no adverse reaction due to medication along with an optimal quality of life for which most patient depend on treatment with antiepileptic drugs (AEDs).[4] A variety of drugs are currently available for the treatment of

epilepsy. The cost of therapy is lower in older/conventional drugs such as phenytoin, carbamazepine, valproic acid, and phenobarbitone; hence, they are commonly used as first-line drugs. Drugs such as levetiracetam, gabapentin, lamotrigine, vigabatrin, topiramate, lacosamide, and zonisamide are the newer ones and currently used as alternative or add-on therapy.[5] Successful therapy is superior in patients with newly diagnosed epilepsy, and the success rate depends on type of seizure, family history, and extent of associated neurological abnormalities. However, currently available AEDs do not completely control seizure activity in some patients and these drugs also frequently produce adverse effects that range in severity from minimal impairment of the central nervous system to death from aplastic anemia or hepatic failure.[6] In spite of the vast array of drugs available monotherapy is normally the first line of treatment, as it has less drug interactions and side effects, lower cost, better tolerability, medication adherence, and quality of life.[5]

Most people with epilepsy are being diagnosed and treated by non-specialists at different levels of health care. In most of such situations, epilepsy management can be suboptimal[5] and with this point of view the present study was designed. The primary objective of this study was to gather information regarding the prescribing pattern of AEDs administered at the outpatient department of a tertiary care teaching hospital, to analyze the possible adverse symptoms if any experienced by the patients, and to analyze and compare the cost of various antiepileptics prescribed.

MATERIALS AND METHODS

Institutional Ethical Committee permission was taken before commencing the study (Approval number: 2018/1/10). The study was a cross-sectional, observational, single centered study conducted at the neurology unit of a tertiary care teaching hospital in Navi Mumbai, Maharashtra, from January 2019 to June 2020. A total of 100 patients who were being prescribed AEDs for seizure disorder presenting themselves at the neurology outpatient were enrolled in the study. Patients of either sex being prescribed antiepileptic drugs for seizure disorders and those willing to participate and give voluntary informed consent were included in the study. Patients <18 years were excluded from the study.

The study consisted of three parts:

### Part I: Analysis of Prescribing Pattern of AEDs for Seizure Disorder

The patients being prescribed AEDs for a seizure disorder in the neurology outpatient department were approached, the purpose and procedure of the study were explained and written informed consent was obtained from them. Data obtained were noted in a case record form and the prescriptions were analyzed for details which included the demographic profile (gender and age) of the patient, condition profile/diagnosis, details of the drugs prescribed and whether the drugs prescribed were according to the WHO core prescribing indicators[7] and if the therapy was according to standard guidelines.[8]

Part II: Analysis of Adverse Drug Reactions of AEDs Prescribed

The patient who was already taking AEDs was asked about any clinical adverse effects and the adverse reactions were analyzed using Naranjo's adverse drug reaction causality scale.[9]

Part III: Cost Analysis of the AEDs Prescribed

The total cost of the drugs per prescription was analyzed. A cost variation analysis was done among the commonly prescribed AEDs. Cost ratio and percentage of cost variation were calculated.
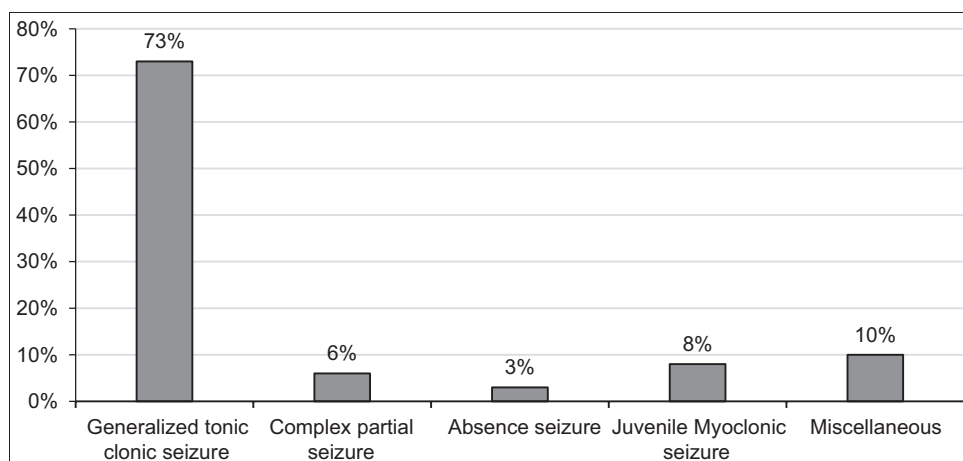
Figure 1: Distribution of diseases

a. "Cost variation[10]
   i. The cost ratio is calculated based on the ratio of the costliest brand to that of the cheapest brand, which is of the same drug
   ii. The formula for the same is as follows: Cost ratio = Price of the costliest brand/Price of the least expensive brand.
b. Percentage cost variation
   i. The percentage cost variation gives an idea about the variation percentage between different brands of the same drug
   ii. The formula for the same is as follows: Percent cost variation = (maximum cost−minimum cost/minimum cost) × 100."

## RESULTS

A total of 100 participants were enrolled in the study. The mean age of the participants was 31.83. The most common age group affected was between 18 and 30 years, followed by 30–45 and >45 [Table 1]. With relation to gender distribution, it was observed that 59% were females and 41% were males. Generalized tonic-clonic seizures (GTCS) (73%) were the most commonly observed, followed by juvenile myoclonic seizures (8%), complex partial seizures (6%), absence seizures (3%), and miscellaneous (10%) [Figure 1]. AEDs

Table 1: Age-wise distribution of the patients

Age-wise distribution	Percentage
18–30	49
30–45	31
>45	20

Table 2: Antiepileptics used as combinations

Drugs used	Frequency	Percentage
Levetiracetam+Benzodiazepine	16	36.3
Carbamazepine+Benzodiazepine	9	20.5
Levetiracetam+Zonisamide	3	6.8
Valproic acid+Topiramate	2	4.5
Carbamazepine+Phenytoin	2	4.5
Carbamazepine+Zonisamide	2	4.5
Carbamazepine+Levetiracetam	6	13.7
Valproic acid+Levetiracetam	4	9.2
Phenytoin+Valproic acid+ Levetiracetam	1	16.7
Carbamazepine+Benzodiazepine+ Levetiracetam	2	33.3
Barbiturate+Phenytoin+Valproic acid	1	16.7
Valproic acid+Benzodiazepine+ Levetiracetam	1	16.7
Phenytoin+Benzodiazepine+ Levetiracetam	1	16.7

commonly prescribed are shown in Figure 2. About 85% of the patients were prescribed medications for 30 days, 8% for 90 days, 5% for 15 days, and 2% for 7 days. Out of the 100 patients given AEDs, 51% were given multitherapy and 49% were given monotherapy, as shown in Figure 3. Drugs prescribed only as monotherapy were levetiracetam (48%), followed by aliphatic carboxylic acid (22%), iminostilbenes (14%), hydantoin (8%), benzodiazepines (4%), and zonisamide (4%) [Figure 4]. In several cases, a combination of AEDs was being, as shown in Table 2. The older AEDs were being combined with newer AEDs. In some cases, >2 AEDs were being used and consisted of cases of GTCS not responding to standard treatment. It was observed that 80.9% of the drugs were prescribed from the National List of Essential Medicines 2015 and 19.10% were not [Figure 5]. Out of the AED drugs prescribed, 96.10% were prescribed by brand name and remaining were by generic name [Figure 6]. The average cost of drugs per prescription was 188.58 INR. The average cost per prescription of the monotherapy drugs most commonly prescribed is levetiracetam (129.53 INR) and valproic acid (134.4 INR). Cost variation analysis was done
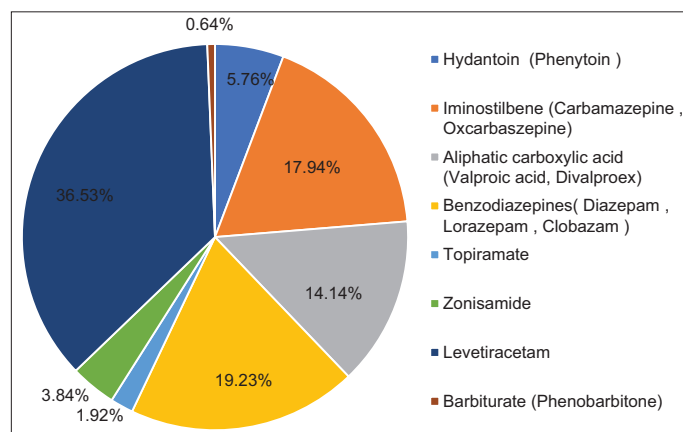
Figure 2: Antiepileptic drugs prescribed

Table 3: Cost variation analysis

Antiepileptic prescribed	Maximum cost (INR)	Minimum cost (INR)	Cost ratio (INR)	Cost variation (%)
Levetiracetam	193.38	129.57	1.49	49.2
Valproic acid	142.33	85	1.67	67.4

Table 4: Naranjo's adverse drug reaction causality scale

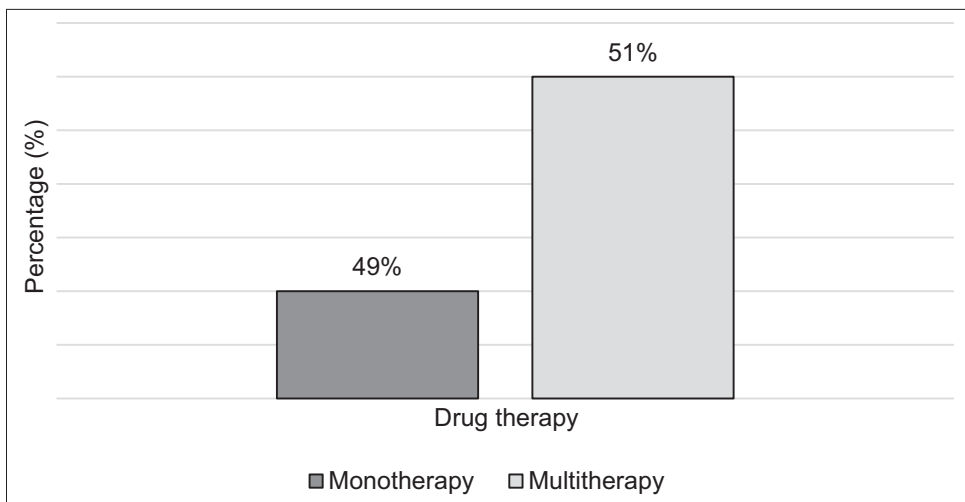| No. of patients	ADR reported	Suspected drug	Causality relationship
1	Drowsiness	Phenytoin	Possible
1	Drowsiness, fatigue, decreased memory and learning, hypertrophy of gums	Phenytoin	Probable
1	Drowsiness	Valproic acid	Possible

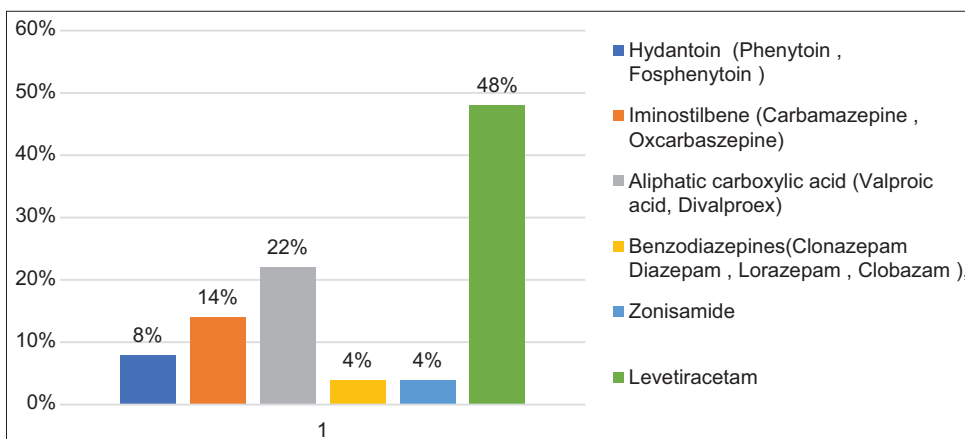**Figure 3:** Multitherapy versus monotherapy in epileptic patients

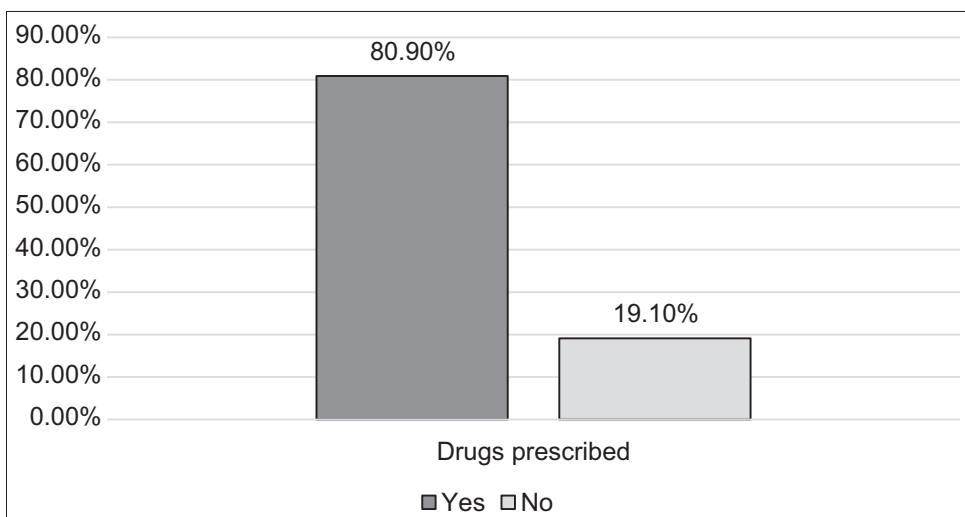**Figure 4:** Drugs prescribed as monotherapy

Figure 5: Drugs prescribed from the National List of Essential Medicines

between the two most commonly prescribed AEDs, as shown in Table 3. Adverse drug reactions were seen in only 3% of the cases. The causality analysis was done using Naranjo's adverse drug reaction causality scale[9] and is described in Table 4.

DISCUSSION

The best manner to treat epilepsy is to establish the diagnosis and only initiate treatment once the diagnosis has been confirmed. The aim of treatment is to control seizures with
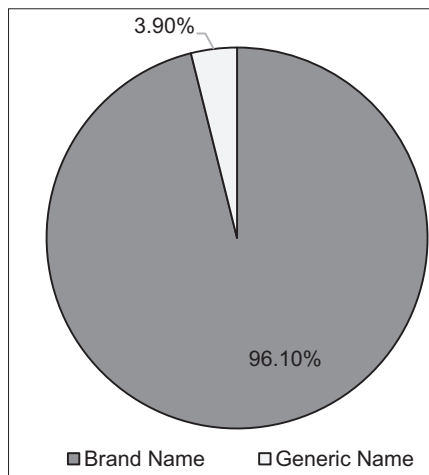
Figure 6: Pattern of drug prescription

the most appropriate AED without causing any significant side effects.[8] In this study, we observed a trend of prescribing newer antiepileptics, satisfactory use of essential medicines and low generic prescribing of drugs.

In our study, the majority of 59% were females and remaining 41% were males. However, other similar studies showed a male preponderance.[11,12] With regard to age distribution, the most common age group affected was between 18 and 30 years with a mean age of 31.83 years. Similar findings were observed in a study conducted by Mane *et al.*[13] In our study, GTCS was found to be the most frequently occurring epilepsy overall. This finding was in accordance with several other studies where GTCS was the most common. [12,14,15] About 49% of the patients were given monotherapy and 51% of the patients were given combination therapy. In our study, >2 drugs were given to a small minority of patients. Most of these were cases of GTCS, uncontrolled on standard therapy. This was similar to the study conducted by Mane *et al.*, in which 38.4% of patients were prescribed monotherapy and remaining patients were prescribed more than two drugs.[13] According to Indian guidelines on epilepsy, treatment should be initiated with one AEDs without changing the formulation of the brand. If the patient does not respond to monotherapy, then the antiepileptic can be changed and the dose of the drug can be slowly built up till the seizure controlled is achieved. Combination therapy should be considered after two attempts at monotherapy have failed.[8] In our study, levetiracetam (36.30%) was the most commonly prescribed antiepileptic followed by iminostilbenes such as carbamazepine, oxcarbazepine (19.70%), benzodiazepines (19.10%), and valproic acid (12.70%). This was different from other studies in which older drugs such as sodium valproate and phenytoin were more preferred.[14-16] The guidelines also recommend the use of older epileptics as first-line drugs for treatment due to lower cost and well-known side effects.[8] However, in this study there was an inclination toward the prescription of newer AEDs along with other older drugs. The reasons for

this could be multiple. In a study conducted by Pohlmann-Eden *et al.*, it was observed that levetiracetam may be considered as a suitable option for initial monotherapy in newly diagnosed epilepsy in some patients due to better tolerability among patients and longer time to treatment withdrawal.[17] In another study conducted by Brodie *et al.*, it was observed that levetiracetam produced equivalent seizure freedom rates in newly diagnosed epilepsy as compared to carbamazepine.[18] On comparison of the total cost of treatment of levetiracetam (129.53 INR) with another standard drug-like valproic acid (134.4 INR) as monotherapy, it was found to be equivalent. Better tolerability and improved compliance among patients due to longer treatment withdrawal time at almost an equivalent cost may be encouraging the prescription of newer AEDs among physicians. The average number of drugs per prescription in our study was 1.57. Similar findings were observed by Patel *et al.*[16] Mane *et al.* observed the average number of drugs to 1.99, which was marginally higher than our study.[13] In our study, the majority (96.10%) of the patients were prescribed drugs by brand name. Only a small minority (3.8%) were prescribed drugs by generic name. In the study conducted by Mane *et al.*, only 8.72% of drugs were prescribed by generic names [13] and in another conducted by Badwaik *et al.* none of the drugs were prescribed by generic name.[12] The average cost per prescription was 188.58 INR. This was higher as compared to the study done by Mane *et al.* in which the average cost per prescription for AEDs was 147.02 INR.[13] Cost variation analysis of the two most commonly prescribed drugs was done, levetiracetam and valproic acid. The cost variation percentage of valproic acid (67.4%) was higher than levetiracetam (49.2%). The prescription of generics along with older AEDs will help reduce the economic burden on the patient. However, other than cost, compliance, and tolerability of drugs among patients must also be taken into consideration while selecting therapy. Lower variation in cost could be an added reason for preference of levetiracetam among physicians, as seen in this study. Adverse drug reactions were observed in 3% of all the total patients. This was similar to a study conducted by Mathur *et al.* in which adverse reactions were observed in 4.67% of the total patients.[5]

There were a few limitations in this study, it was a cross-sectional study and the patients were not followed up after the visit to evaluate the long-term safety and efficacy of the AEDs prescribed. The study included only patients from the outpatient department and indoor patients were not included. Regular follow-up and including indoor patients in future studies will open up the possibility of obtaining more adverse reactions. It was a single centered study and sample size was limited. A larger sample size, conducted in several centers will be more beneficial. In this study, we did not measure the indirect costs of the patient. Further studies can be undertaken in these areas to get a better understanding of the financial burden on the patient.

CONCLUSION

Physician selection of drugs depends on several factors such as drug tolerability, patient compliance, efficacy of treatment, and cost of therapy. This study documented a rise in the prescribing trend of newer antiepileptics. The selection of essential drugs was high; however, there is a need to emphasize the concept of prescribing generic medicine among physicians, which will help in lowering the total cost of therapy for patients.

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